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Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults (Review)

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Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010609.
DOI: 10.1002/14651858.CD010609.

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[Intervention Review]

Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 5, 2016.

Citation: Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD010609. DOI: 10.1002/14651858.CD010609.

ABSTRACT

Background

Some antiepileptic drugs but not others are useful in clinical practice for the prophylaxis of migraine. This might be explained by the variety of actions of these drugs in the central nervous system. The present review is part of an update of a Cochrane review first published in 2004, and previously updated (conclusions not changed) in 2007.

Objectives

To describe and assess the evidence from controlled trials on the efficacy and tolerability of gabapentin/gabapentin enacarbil or pregabalin for preventing migraine attacks in adult patients with episodic migraine.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2012, Issue 12), PubMed/MEDLINE (1966 to 15 January 2013), MEDLINE In-Process (current week, 15 January 2013), and EMBASE (1974 to 15 January 2013) and handsearched *Headache* and *Cephalalgia* through January 2013.

Selection criteria

Studies were required to be prospective, controlled trials of gabapentin/gabapentin enacarbil or pregabalin taken regularly to prevent the occurrence of migraine attacks, to improve migraine-related quality of life, or both.

Data collection and analysis

Two review authors independently selected studies and extracted data. For headache frequency data, we calculated mean differences (MDs) between gabapentin and comparator (placebo, active control, or gabapentin in a different dose) for individual studies and pooled these across studies. For dichotomous data on responders (patients with ≥ 50% reduction in headache frequency), we calculated odds ratios (ORs) and numbers needed to treat (NNTs). We also summarised data on adverse events from all single dosage studies and calculated risk differences (RDs) and numbers needed to harm (NNHs).

Main results

Five trials on gabapentin and one trial on its prodrug gabapentin enacarbil met the inclusion criteria; no reports on pregabalin were identified. In total, data from 1009 patients were considered. One trial each of gabapentin 900 mg (53 patients), and gabapentin titrated to 1200 mg (63 patients) and 1800 mg (122 patients) failed to show a statistically significant reduction in headache frequency in the active treatment group as compared to the placebo group, whereas one trial of gabapentin titrated to 1800 to 2400 mg (113 patients) demonstrated a small but statistically significant superiority of active treatment for this outcome (MD -0.80; 95% confidence interval (CI) -1.55 to -0.05). The pooled results of these four studies (MD -0.44; 95% CI -1.43 to 0.56; 351 patients) do not demonstrate a significant difference between gabapentin and placebo. One trial of gabapentin titrated to 1800 mg (122 patients) failed to demonstrate a significant difference between active treatment and placebo in the proportion of responders (OR 0.97; 95% CI 0.45 to 2.11), whereas one trial of gabapentin titrated to 1800 to 2400 mg (113 patients) demonstrated a small but statistically significant superiority of active treatment for this outcome (OR 2.79; 95% CI 1.09 to 7.17). The pooled results of these two studies (OR 1.59; 95% CI 0.57 to 4.46; 235 patients) do not demonstrate a significant difference between gabapentin and placebo. Comparisons from one study (135 patients) suggest that gabapentin 2000 mg is no more effective than gabapentin 1200 mg. One trial of gabapentin enacarbil (523 participants) failed to demonstrate a significant difference versus placebo or between doses for gabapentin enacarbil titrated to between 1200 mg and 3000 mg with regard to proportion of responders; there was also no evidence of a dose-response trend. Adverse events, most notably dizziness and somnolence, were common with gabapentin.

Authors' conclusions

The pooled evidence derived from trials of gabapentin suggests that it is not efficacious for the prophylaxis of episodic migraine in adults. Since adverse events were common among the gabapentin-treated patients, it is advocated that gabapentin should not be used in routine clinical practice. Gabapentin enacarbil is not efficacious for the prophylaxis of episodic migraine in adults. There is no published evidence from controlled trials of pregabalin for the prophylaxis of episodic migraine in adults.

PLAIN LANGUAGE SUMMARY

Gabapentin or pregabalin for preventing migraine attacks in adults

Various medicines, collectively termed 'antiepileptics', are used to treat epilepsy. For several years, some of these drugs have also been used for preventing migraine attacks. For the present review, researchers in The Cochrane Collaboration reviewed the evidence about the effects of gabapentin and two related drugs (pregabalin and gabapentin enacarbil) in adult patients (≥ 16 years of age) with 'episodic' migraine (headache on < 15 days per month). They examined research published up to 15 January 2013, along with three unpublished and previously confidential drug company research reports, and found six relevant studies, five of gabapentin and one of gabapentin enacarbil, both over a wide dose range. The studies showed that neither gabapentin nor gabapentin enacarbil was more effective than placebo at reducing the frequency of migraine headaches. Gabapentin commonly caused side effects, especially dizziness and somnolence (sleepiness). No studies of pregabalin were identified, and research on this drug is desirable.

BACKGROUND

Description of the condition

Migraine is a common and disabling health problem among children and predominantly young and middle-aged adults. Surveys from the main regions of the world suggest that the global prevalence of migraine is 14.7% (18.8% among women and 10.7% among men) (GBD 2010 Study). This disorder results in significant disability and work loss, and several studies have addressed the issue of the costs of migraine. In one of the most recent publications, aggregate direct and indirect costs to society due to migraine among adults in the European Union were estimated to amount to 50 billion Euros (67 billion US dollars) annually, or about 1222 Euros (1634 US dollars) annually per sufferer (Linde 2012).

Description of the intervention

Drug therapy for migraine falls into two categories: acute and preventive. Acute therapy aims at the symptomatic treatment of the head pain and other symptoms associated with an acute attack of migraine. The primary goals of preventive treatment are to reduce attack frequency, severity, and duration. Moreover, such therapy is commonly employed in an attempt to improve responsiveness to acute treatment, enhance functional status, and reduce disability. Evidence-based guidelines on the drug treatment of migraine have been developed and published by the European Federation of Neurological Societies (EFNS; Evers 2009). These guidelines suggest that prophylactic therapy should be considered for patients with migraine when quality of life, business duties, or school attendance are severely impaired; when the frequency of attacks is two or more per month; when there is a lack of response to acute drug treatment; and when frequent, very long, or uncomfortable auras occur.

This review considers the evidence for the efficacy and tolerability of the antiepileptic drugs gabapentin and pregabalin for preventing episodic migraine in adults. The prophylactic treatment of migraine in children is the subject of a separate Cochrane review (Victor 2003).

Gabapentin (systematic name 2-[1-(aminomethyl)cyclohexyl]acetic acid) was originally synthesised to mimic the chemical structure of the neurotransmitter gamma-aminobutyric acid (GABA). Following oral administration, peak plasma concentration of gabapentin is reached within two to three hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. The absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics. The distribution volume for women is approximately 50% that of men. There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic enzymes responsible for drug metabolism. Gabapentin is excreted exclusively by the kidneys in unchanged form. The elimination half-life of gabapentin is independent of dose and averages five to seven hours. In elderly patients and patients with impaired renal function, gabapentin plasma clearance is reduced.

Gabapentin enacarbil is a prodrug for gabapentin. It was designed for increased oral bioavailability over gabapentin, and human trials showed it to produce extended release of gabapentin with almost twice the overall bioavailability, especially when taken with a fatty meal. Even in the therapeutic range, the intestinal absorption mechanisms of gabapentin are readily saturated, which impedes bioavailability of the drug. This does not pertain to gabapentin enacarbil. Due to the enhanced absorption of gabapentin enacarbil compared to gabapentin, the two drugs are not dose equivalent.

Pregabalin is related in structure to gabapentin. Compared to gabapentin, pregabalin is more potent, more quickly absorbed, and has greater bioavailability.

How the intervention might work

We use the term 'antiepileptics' here to refer generally to those drugs in common use for the treatment of epilepsy. The pharmacological treatment of epilepsy can be traced back as far as 1857, but the period of greatest development of antiepileptics was between 1935 and 1960, when 13 drugs were developed and marketed (Porter 1992). In recent decades, renewed interest has led to the development of several novel antiepileptics which may confer advantages in tolerability (Dalkara 2012), and these are beginning to be used in migraine also.

The use of antiepileptics for the prophylactic treatment of migraine is theoretically warranted by several known modes of action which relate either to the general modulation of pain systems or more specifically to systems involved in the pathophysiology of migraine (Silberstein 2008; Wiffen 2010). It is necessary to point out, however, that it is still not possible to state with any certainty which particular mode or modes of action of antiepileptics are relevant to the prophylaxis of migraine. The evidence is against these drugs, to the extent that they are a class. Only two antiepileptics (topiramate and valproate) out of 12 scientifically investigated for migraine prophylaxis have shown unequivocal efficacy, and it is not known how these are different from the others.

Why it is important to do this review

Some antiepileptic drugs are marketed specifically for migraine prophylaxis. The EFNS (Evers 2009) and the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society (Silberstein 2012) list topiramate and valproic acid among first-line migraine prophylactics. Regarding gabapentin, the EFNS lists it as a drug of third choice (only probable efficacy; Evers 2009), and the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society (Silberstein 2012) list it as Level U (inadequate or conflicting data to support or refute medication use). By contrast, a strong recommendation for the use of gabapentin for the prophylaxis of episodic migraine was recently given by the Canadian Headache Society Prophylactic Guidelines Development Group (Pringsheim 2012). The above-mentioned guidelines do not comment specifically on gabapentin enacarbil or pregabalin.

There is a fairly substantial body of evidence from controlled trials supporting the efficacy of many of the agents used for preventing migraine, yet such therapies are used by only a small percentage of patients with migraine — 3% to 12% in various studies (Clarke 1996; Edmeads 1993; Mehuys 2012). It is hoped that this review and others like it will increase awareness of migraine prophylactic treatment options and help to provide a systematic basis for making the best possible choice of such therapy in those individuals in need of it.

The present review is part of a series of reviews which, taken together, represent an update of a Cochrane review on 'Anticonvulsant drugs for migraine prophylaxis' (Chronicle 2004; Mulleners 2008; first published in 2004, and previously updated (conclusions not changed) in 2007). The old review has been split into four separate reviews for updating:

1. Topiramate for the prophylaxis of episodic migraine in adults (Linde 2013a)
2. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults (Linde 2013b)
3. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults (the present review; Linde 2013c)
4. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults (Linde 2013d)

Unpublished data from industry-sponsored clinical trials that tested the efficacy of gabapentin for off-label use in migraine have recently entered the public domain, not through the usual channels of scientific publication, but through the legal process in two recent US litigations against the sponsor (Landefeld 2009; Saris 2010). Three randomised clinical trials of gabapentin versus placebo are documented in internal company research reports, which are standardised documents prepared by or for the sponsor. These reports describe the research conducted using a standardised format similar to that of a scientific manuscript, but in much greater detail, and may include the study protocol and protocol amendments, a listing and description of adverse events, data analyses, and a statistical analysis plan.

One of the three migraine research reports was never published, but the other two correspond in some way to publications in the peer-reviewed literature. Important discrepancies between the results described in the research reports and the corresponding published manuscripts have been noted (Vedula 2009). One of us obtained and examined the migraine prophylaxis research reports as an expert witness in one of the US litigations (McCrory 2008).

Of the three randomised clinical trials of gabapentin versus placebo that are included among these data:

1. Study 945-220, described in RR 995-00074, corresponds to a full-length publication (Mathew 2001) which, however, misrepresents the findings in RR 995-00074.
2. Study 879-200, described in RR 4301-00066, was partially reported in abstract form (Wessely 1987 — appears to be an interim analysis), but was never published in full or final form.
3. Study 945-217, described in RR 995-00085, was never published in any form.

In addition to these new data, we also obtained unpublished data from a published trial (Di Trapani 2000) through correspondence with the senior author (Prof Alessandro Capuano).

The addition of all of these new data augments our previous review substantially and markedly changes the conclusions. In the previous review (Chronicle 2004; Mulleners 2008), we expressed cautious support for gabapentin, as follows:

"The evidence derived from trials of gabapentin suggests a beneficial effect in migraine prophylaxis, but this drug needs further evaluation. Although three clinical trials of reasonable size have been reported, the interpretation of two [Di Trapani 2000; Mathew 2001] is hampered by some aspects of their method or data analysis, while the third [Jimenez 1999] does not provide unequivocal evidence for efficacy, as it is primarily a dose comparison study. In the meantime, it may be advocated with some reservation that gabapentin may be used for those cases that are difficult to manage with other currently available strategies, since it has a reasonable tolerability and safety profile."

After incorporation of the previously unpublished data, this updated review now suggests with more certainty that gabapentin does not meet the standard of a statistically significant benefit in reducing migraine frequency.

OBJECTIVES

To describe and assess the evidence from controlled trials on the efficacy and tolerability of gabapentin/gabapentin enacarbil or pregabalin for preventing migraine attacks in adult patients with episodic migraine.

METHODS

Criteria for considering studies for this review

Types of studies

The International Headache Society (IHS) has provided a useful document setting out guidelines for the conduct of clinical trials in migraine, to which current investigators are encouraged to adhere (Tfelt-Hansen 2012). This document was not used as the sole basis for considering studies in this review, as too many potentially informative past studies would likely have been excluded on methodological grounds. However, many of its recommendations have been used as a basis for what follows.

Included studies were required to be prospective, controlled trials of self administered gabapentin or pregabalin taken regularly to prevent the occurrence of migraine attacks, to improve migraine-related quality of life, or both. We included trials only if allocation to treatment groups was randomised or pseudo-randomised (based on some non-random process unrelated to the treatment selection or expected response). Blinding was not required. We excluded concurrent cohort comparisons and other non-experimental designs.

Types of participants

Study participants were required to be adults (at least 16 years of age) and to meet reasonable criteria designed to distinguish migraine from tension-type headache. If patients with both types of headache were included in a trial, results were required to be stratified by headache diagnosis. We did not require the use of a specific set of diagnostic criteria (eg, Ad Hoc Cttee 1962; IHS Cttee 1988; ICHD-II 2004), but migraine diagnoses had to be based on at least some of the distinctive features of migraine, eg, nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. Secondary headache disorders had to be excluded using reasonable criteria.

We anticipated that some of the trials identified would include patients described as having mixed migraine and tension-type headaches or combination headaches, and the protocol for this review described detailed procedures for dealing with such trials. In the end, no such precautions were necessary. We excluded studies evaluating treatments for chronic daily headache, chronic migraine, and transformed migraine. The reasons for this are: (a) the definition of chronic migraine is still heavily debated, and a revision of the 2004 IHS criteria for this condition has been proposed (Olesen 2006); (b) transformed migraine and chronic daily headache, although commonly used terms, are insufficiently validated diagnoses; (c) the separation of these conditions from headache due to medication overuse is not always clear in many studies; and (d) there is some evidence that suggests that chronic migraine may be more refractory to standard prophylactic treatment than episodic migraine. We explicitly excluded trials and treatment groups including only patients with tension-type headache.

Types of interventions

Included studies were required to have at least one arm in which gabapentin or pregabalin (without concomitant use of other migraine prophylactic treatment) was given regularly during headache-free intervals with the aim of preventing the occurrence of migraine attacks, improving migraine-related quality of life, or both. Acceptable comparator groups included placebo, no intervention, active drug treatment (ie, with proven efficacy, not experimental), the same drug treatment with a clinically relevant different dose, and non-pharmacological therapies with proven efficacy in migraine. The analysis included only drugs and dosages that are commercially available.

We recorded any data reported on treatment compliance in the Characteristics of included studies table. After examination of these data, it did not seem necessary to stratify the analysis by compliance.

We anticipated that most trials would permit the use of medication for acute migraine attacks experienced during the trial period. We therefore recorded descriptions of trial rules concerning the use of acute medication in the Characteristics of included studies table whenever such information was provided. We did not otherwise model or adjust for this factor in our analysis.

Types of outcome measures

We collected and analysed trial data on headache frequency, responders (patients with ≥ 50% reduction in headache frequency), quality of life, and adverse events.

Search methods for identification of studies

Search strategies used in our earlier review (Chronicle 2004; Mulleners 2008) are detailed in Appendix 1 (last search date 31 December 2005). For the present update, trained information specialists developed detailed search strategies for each database searched (Appendix 2). The new searches overlapped the old searches by a full year to ensure complete coverage. The last search date for all updated searches was 15 January 2013.

Databases searched for this update were:

- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2012, Issue 12; years searched = 2005 to 2012);
- MEDLINE (via OVID), 2005 to 15 January 2013;
- MEDLINE In-Process (via OVID), current week, 15 January 2013;
- EMBASE (via OVID), 2005 to 15 January 2013.

Additional strategies for identifying trials included searching the reference lists of review articles and included studies, searching books related to headache, and consulting experts in the field. We attempted to identify all relevant published trials, irrespective of language. We handsearched two journals, *Headache* and *Cephalalgia*, in their entirety through January 2013.

Data collection and analysis

Selection of studies

Two of us independently screened titles and abstracts of studies identified by the literature search for eligibility. Papers that could not be excluded with certainty on the basis of information contained in the title and/or abstract were retrieved in full for screening. Disagreements were resolved through discussion. We retrieved papers passing this initial screening process, and two of us independently reviewed the full texts. Disagreements at the full-text stage were resolved through internal discussion and, in a few cases, through correspondence with members of the editorial staff of the Cochrane Pain, Palliative and Supportive Care Review Group. We were not blinded to study investigators' names and institutions, journal of publication, or study results at any stage of the review.

The search strategy described above identified a large number of short conference and journal abstracts. The majority of these either (a) reported partial results of ongoing trials; (b) provided insufficient information on trial design or results; (c) were early reports of included studies; or (d) were reproductions of abstracts of papers published in full (for example, the journal *Headache* reproduces abstracts of interest to readers, and these are found by PubMed). We agreed that short abstracts of this kind would be excluded from consideration.

Data extraction and management

Two of us independently abstracted information on patients, methods, interventions, efficacy outcomes, and adverse events from the original reports onto specially designed, pre-tested paper forms. Disagreements were again resolved through discussion.

We anticipated that trials would vary in length, that outcomes would be measured over various units of time (eg, number of attacks per two weeks versus number of attacks per four weeks), and that results would be reported for numerous different time points (eg, four-week headache frequency at two months versus at four months). We attempted to standardise the unit of time over which headache frequency was measured at 28 days (four weeks) wherever possible. We recorded outcomes beginning four weeks after the start of treatment and continued through all later assessment periods. We made decisions about which time points to include in the final analysis once the data had been collected.

We anticipated that outcomes measured on a continuous scale (eg, headache frequency) would be reported in a variety of ways, eg, as mean pre-treatment, post-treatment, and/or change scores. Among change scores, we preferred the mean of within-patient changes (from baseline to on-treatment in a parallel-group trial) over the change in group means because the first both results in a lower variance (taking into account the correlation between

baseline and post-treatment scores in each patient) and adjusts for imbalances in baseline headache frequencies, while the latter has only the second advantage. When neither type of change score was reported, we compared post–treatment means between groups, assuming that baseline data would be balanced due to randomisation. We anticipated that many trials would report group means, without reporting data on the variance associated with these means. In such cases, we attempted to calculate or estimate variances based on primary data, test statistics, and/or error bars in graphs.

When efficacy outcomes were reported in dichotomous form (success/failure), we required that the threshold for distinguishing between treatment success and failure be clinically significant; for example, we interpreted a ≥ 50% reduction in headache frequency as meeting this criterion. In such cases, we recorded, for each treatment arm, the number of patients included in the analysis and the number with each outcome.

The protocol for this review specified rules for dealing with outcome data reported on an ordinal scale (eg, for reduction in headache frequency: 0%, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, 100%) but, in fact, none of the included trials reported ordinal data for outcomes of interest.

We envisaged that the preferred methods of collecting and presenting data on quality of life would most likely be the Migraine-Specific Questionnaire (MSQ) and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). However, other instruments and other types of outcomes related to quality of life (eg, work absenteeism) were not excluded a priori, and these data were kept under review before specifying rules for analysing outcome data in this domain.

We recorded the proportion of patients reporting adverse events for each treatment arm wherever possible. The identity and rates of specific adverse events were also recorded. We anticipated that reporting of adverse events would vary greatly across trials with regard to the terminology used, method of ascertainment, and classification of adverse events as drug-related or not and as severe or not.

Assessment of risk of bias in included studies

We completed a 'Risk of bias' table for each study, using assessments of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). For new studies identified in the present update, two of us completed this assessment independently; for older studies, one of us performed the assessment and a second author reviewed and commented on it. Disagreements were resolved through discussion.

We also assessed the methodological quality of individual trials using the scale devised by Jadad and colleagues (Jadad 1996), operationalised as follows:

1. Was the study described as randomised? (1 = yes; 0 = no)
2. Was the method of randomisation well described and adequate? (0 = not described; 1 = described and adequate; -1 = described, but not adequate)
3. Was the study described as double-blind? (1 = yes; 0 = no)
4. Was the method of double-blinding well described and adequate? (0 = not described; 1 = described and adequate; -1 = described, but not adequate)
5. Was there a description of withdrawals and dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial? (1 = yes; 0 = no)

Each trial thus received a score of 0 to 5 points, with higher scores indicating higher quality in the conduct or reporting of the trial. Two review authors scored the studies independently, and a consensus score was then arrived at through discussion. The consensus score is reported for each study in the Characteristics of included studies table and was not used as a weighting in statistical analyses.

Measures of treatment effect

The primary outcome considered for the efficacy analysis was headache frequency. Among headache frequency measures, we preferred number of migraine attacks to number of days with migraine. The latter measure confusingly incorporates attack duration into the measure of headache frequency. Moreover, attack duration is affected by the use of symptomatic medication, which is permitted in most trials. We also analysed headache frequency in terms of a responder rate, or the proportion of patients with a ≥ 50% reduction in headache frequency from pre- to post-treatment.

As noted above (Data extraction and management), we kept patient-reported quality of life data under review as studies were selected. The only quality of life data available for a rigorous analysis were measured, in RR 995-00085, by the SF-36 (nine domains).

The analysis considered only outcome data obtained directly from the patient and not those judged by the treating physician or study personnel. Efficacy data based on contemporaneous and timed (usually daily) recording of headache symptoms were preferred to those based on global or retrospective assessments.

In addition, we tabulated adverse events for each included study.

Unit of analysis issues

In the case of cross-over trial designs, we anticipated that the data reported would normally not permit analysis of paired within-patient data. We thus planned to analyse cross-over trials as if they were parallel-group trials, combining data from all treatment periods. In fact, none of the included trials used a cross-over design.

Dealing with missing data

Where data were missing or inadequate, we attempted to obtain these data by correspondence with study authors.

Assessment of heterogeneity

We tested estimates of efficacy (both mean differences (MDs) and odds ratios (ORs)) for homogeneity. When significant heterogeneity was present, we made an attempt to explain the differences based on the clinical characteristics of the included studies. We did not statistically combine studies that were clinically dissimilar. However, when a group of studies with statistically heterogeneous results appeared to be clinically similar, we did combine study estimates. We performed all pooled analyses using a random-effects model.

As a sensitivity analysis, we also planned to calculate a pooled effect estimate using a fixed-effect model for major outcomes (headache frequency, responder rate, and any adverse event) when the random-effects result was near-significant ($0.05 \leq P \leq 0.15$) and the pooled studies were homogeneous (heterogeneity statistics: $P > 0.15/I^2 < 30\%$). Such a sensitivity analysis would evaluate whether conclusions might differ based on the statistical model used for pooling in situations where a fixed-effect model might reasonably be considered instead of a random-effects model. In fact, however, no such sensitivity analyses were warranted in the present review.

Data synthesis

We anticipated that continuous outcome measures of headache frequency would be reported on different and often incompatible scales. Although we attempted to standardise the extraction of headache frequency data to a 28-day (four-week) period, this was not possible in every case. In our previous review (Chronicle 2004; Mulleners 2008), we therefore analysed these data using the standardised mean difference (SMD, with 95% confidence intervals (CIs)) rather than the mean difference (MD). The introduction of change scores in the newly included studies for some of the reviews in this series necessitated a change in the analysis plan from SMDs to MDs. The latter also has the advantage of giving a result in clinically meaningful units (ie, x fewer migraines per 28 days).

We used dichotomous data meeting our definition of a clinically significant threshold to calculate odds ratios (ORs), with 95% CIs. We additionally computed numbers needed to treat (NNTs), with 95% CIs, as the reciprocal of the risk difference (RD) versus placebo (McQuay 1998).

In the same way, we used data on the proportion of patients reporting adverse events to calculate RDs and numbers needed to harm (NNHs).

We analysed data on gabapentin and gabapentin enacarbil separately, since the two drugs are not dose equivalent.

Subgroup analysis and investigation of heterogeneity

We considered subgroup analyses undertaken by dose, method of randomisation, and by completeness of blinding, but did not undertake them because of insufficient data.

RESULTS

Description of studies

Results of the search

The PubMed search strategy for our previous review (Chronicle 2004; Mulleners 2008) yielded 1089 potentially eligible citations, while the EMBASE and CENTRAL searches yielded 290 and 6952 citations, respectively. No additional citations were retrieved from the Cochrane Pain, Palliative & Supportive Care Trials Register or from other sources. After title and abstract screening, we obtained 58 published papers on antiepileptics for full-text scrutiny. Of these, eight (three included, five excluded) investigated gabapentin. No paper investigated pregabalin.

The MEDLINE search strategy for the present update (from 2005 on) yielded 188 citations as possible candidates for the current series of reviews on antiepileptic drugs for migraine prophylaxis; the search of MEDLINE In-Process identified an additional 20 citations. The EMBASE and CENTRAL updates identified 484 and 85 citations, respectively. After title and abstract screening, we obtained 37 published papers on antiepileptics for full-text scrutiny. Of these, none investigated gabapentin or pregabalin, and one (included) investigated gabapentin enacarbil.

In addition, as described above (Why it is important to do this review), three previously confidential research reports (RR 4301-00066; RR 995-00074; RR 995-00085) investigating gabapentin recently became public by virtue of being entered into evidence in a legal proceeding in 2008. All three are included here. The inclusion of RR 995-00074 led to the exclusion of Mathew 2001 (see Characteristics of excluded studies), which was included in our previous review (Chronicle 2004; Mulleners 2008).

Thus, for the present update, we reviewed a total of 12 papers (nine published and three unpublished) at the full-text screening stage. Of these, we included six papers and excluded six.

Included studies

The six included papers reported data from six unique studies, including five that compared gabapentin (Di Trapani 2000; RR 4301-00066; RR 995-00085; RR 995-00074) or gabapentin enacarbil (Silberstein 2013) to placebo, and two that generated data that enabled dose comparisons of gabapentin (Jimenez 2002) or gabapentin enacarbil (Silberstein 2013). No trial compared gabapentin to another active intervention.

All six trials had a parallel-group design.

The doses of gabapentin investigated in the trials were 900 to 2400 mg/day. This can be compared to the range of doses used in epilepsy, which is 900 to 3600 mg/day.

The doses of gabapentin enacarbil investigated in the trial were 1200 to 3000 mg/day. This drug is not approved by the FDA for the treatment of epilepsy but rather for the treatment of moderate-to-severe restless legs syndrome and postherpetic neuralgia in adults. The standard dosing for treatment of restless legs syndrome is 600 mg/day.

The median duration of the treatment phase of the included trials was 12 weeks (mean 14; range 12 to 20 weeks).

See Characteristics of included studies for further details.

Excluded studies

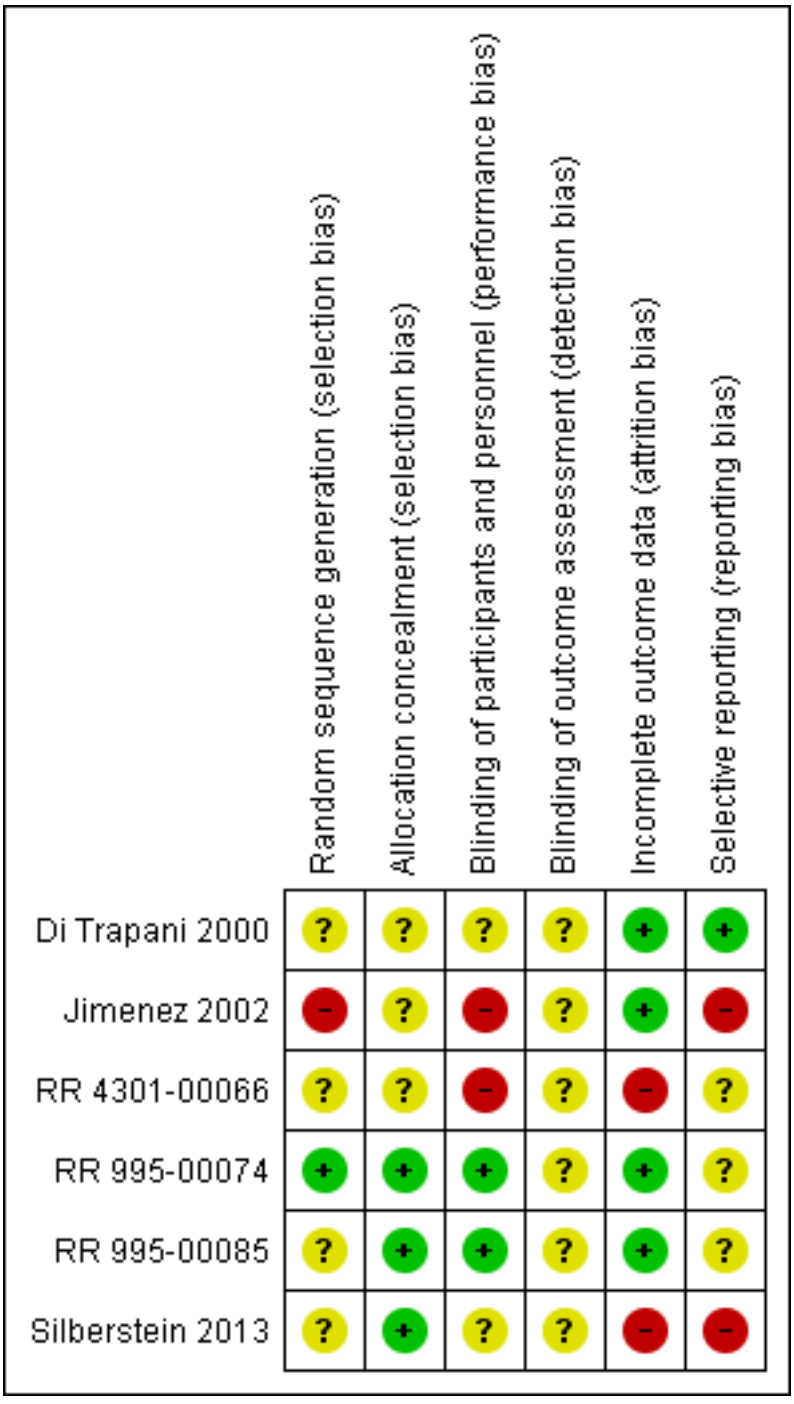
Of the 12 papers obtained for full-text scrutiny, six were excluded for reasons given in the Characteristics of excluded studies table.

Risk of bias in included studies

We scored methodological quality using the Jadad scale as indicated in the Assessment of risk of bias in included studies section, with a maximum attainable score of 5. The median quality score was 4 (mean 3.7; range 2 to 5).

Of 36 risk of bias items scored for the six studies, the majority of ratings were either 'unclear' (18 (50%)) or 'low' (11 (31%); we judged three studies (Di Trapani 2000; RR 4301-00066; Silberstein 2013) as having a 'high' risk of bias for two or more items (Figure 1).

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only one of the six studies provided an adequate methodological description of how allocation sequences were generated (by a computer-generated randomisation schedule), and only three provided an adequate methodological description of attempts to conceal allocation of intervention assignment (see Figure 1 and the Characteristics of included studies table). We judged that there was a high risk of selection bias for Jimenez 2002, where the very unequal numbers of patients in the two dosage groups are unlikely to have been achieved by strict randomisation.

Blinding

Participants and clinicians were reported as blinded during the conduct of five of the six studies (see Characteristics of included studies table). The procedure described for double-blinding in RR 4301-00066, RR 995-00085, and RR 995-00074 was packaging and labelling identical-appearing tablets according to the randomisation codes. However, given that the number of gabapentin subjects erroneously receiving other prophylaxis in RR 4301-00066 was nearly three times higher in the gabapentin group than in the placebo group, it is likely that the blinding was

inadequate. Details of the methodology used were not reported for Di Trapani 2000. Jimenez 2002 was an open-label trial and therefore also suffers from a high risk of performance bias. We judged the risk of detection bias as unclear in all studies, since none explicitly stated blinding of outcome assessment.

Incomplete outcome data

Completeness of data was adequately reported for four studies (Figure 1). Usually an intention-to-treat (ITT) analysis was applied (see the Characteristics of included studies table). We were concerned about the high number of protocol violators due to the initiation or continuation of other prophylactics (19 of those allocated to gabapentin; seven of those allocated to placebo) in RR 4301-00066. It is not clear whether the majority initiated other prophylaxis prior to or after randomisation. The higher efficacy means in the gabapentin ITT population (with violators) compared to the efficacy population (without violators) suggest that a significant number may have been initiated after randomisation, possibly because of lack of efficacy. Only the data for the smaller efficacy population of RR 4301-00066 are included in this review. We used the modified intention-to-treat (mITT) and safety evaluable populations for analysis of efficacy outcomes and adverse events, respectively, in RR 995-00074; RR 995-00085. In Silberstein 2013, subjects were randomised despite missing baseline values.

Selective reporting

We judged the risk of reporting bias as low only in Di Trapani 2000. The senior author confirmed that statistical variance estimates reported in the paper were standard errors of the mean (SEMs) and provided additional unpublished data for this review. It is remarkable that the negative results in the research reports of RR 4301-00066 and RR 995-00085 were classified as confidential and would have remained unobtainable had it not been for the discovery process in a legal case. Reporting bias is obvious in Jimenez 2002, since adverse events are not reported separately for each group. Within-group changes (with standard deviations (SDs)) from baseline in mean migraine frequencies during the double-blind period were lacking in Silberstein 2013 and were not provided upon request to the corresponding author.

Other potential sources of bias

Statistically significant results are more likely to be published than trials affirming a null result. The tendency for negative or inconclusive results to remain unpublished has been particularly problematic in the context of the present review, and there is no guarantee that other unpublished studies do not exist.

Effects of interventions

Gabapentin or gabapentin enacarbil versus placebo

Methodological considerations

Although there was methodological variation, as described above (Risk of bias in included studies), the included trials were fundamentally similar with regard to basic design, patients, and measures.

All doses reported below are given in terms of mg/day.

Headache frequency

One trial each of gabapentin in a stable dose of 900 mg (RR 4301-00066; 53 patients), titrated to 1200 mg (Di Trapani 2000; 63 patients), and titrated to 1800 mg (RR 995-00085; 122 patients) failed to show a statistically significant reduction in headache frequency with active treatment compared to placebo, whereas one trial of gabapentin titrated to 1800 to 2400 mg (RR 995-00074; 113 patients) demonstrated a small but statistically significant superiority of active treatment over placebo for this outcome (mean difference (MD) -0.80; 95% confidence interval (CI) -1.55 to -0.05). The pooled results of these four studies (MD -0.44; 95% CI -1.43 to 0.56; 351 patients) do not demonstrate a significant difference between gabapentin and placebo (Analysis 1.1). To put the above MD estimates into context, the median baseline headache frequency in the gabapentin groups of the four placebo-controlled trials was 5.1 attacks per 28 days (mean 5.1; range: 4.9 to 6.1).

The sole trial of gabapentin enacarbil versus placebo (Silberstein 2013) did not report sufficient data for us to calculate MDs for this outcome.

Responders (patients with ≥ 50% reduction in headache frequency)

One trial of gabapentin titrated to 1800 mg (RR 995-00085; 122 patients) failed to demonstrate a significant difference between active treatment and placebo in the proportion of responders (odds ratio (OR) 0.97; 95% CI 0.45 to 2.11), whereas one trial of gabapentin titrated to 1800 to 2400 mg (RR 995-00074; 113 patients) demonstrated a small but statistically significant superiority of active treatment over placebo for this outcome (OR 2.79; 95% CI 1.09 to 7.17). The pooled results (OR 1.59; 95% CI 0.57 to 4.46; 235 patients) do not support an effect of gabapentin (Analysis 1.2).

One trial of gabapentin enacarbil (Silberstein 2013) failed to demonstrate a significant difference between the active drug titrated to 1200 mg (59 patients), 1800 mg (114 patients), 2400 mg (123 patients), or 3000 mg (58 patients), and placebo (120 patients) in the proportion of responders (Analysis 2.1).

Quality of life

The only quality of life data available in the included trials were comparisons between gabapentin 1800 mg and placebo in nine dimensions of the SF-36 (RR 995-00085). Because these two interventions did not differ significantly with regard to reduction of headache frequency, we undertook no further analyses of these data.

Dose comparisons for gabapentin or gabapentin enacarbil

Jimenez 2002 (135 patients) compared gabapentin 1200 mg and 2000 mg. There were no significant differences between the groups, either in headache frequency (MD -0.50; 95% CI -1.11 to 0.11; Analysis 3.1) or in the proportion of responders (OR 0.89; 95% CI 0.41 to 1.91; Analysis 3.2).

Silberstein 2013 compared gabapentin enacarbil 1200 mg (59 patients), 1800 mg (114 patients), 2400 mg (123 patients), and 3000 mg (58 patients). Data were insufficient for us to calculate MDs for headache frequency, our preferred outcome measure. There were no significant differences between the groups in the proportion of responders (Analysis 4.1).

Safety

Safety data from placebo-controlled trials of gabapentin and gabapentin enacarbil are summarised in Table 1 and Table 2, respectively. For gabapentin, we calculated risk differences (RDs) versus placebo for any adverse event (Analysis 1.3) and for each of the five most prevalent adverse events, namely, asthenia/fatigue (Analysis 1.4), dizziness (Analysis 1.5), flu syndrome (Analysis 1.6), somnolence (Analysis 1.7), and abnormal thinking (Analysis 1.8). Numbers needed to harm (NNHs; with 95% CIs) for the pooled analyses of gabapentin 900 to 2400 mg versus placebo were as follows:

- Any adverse event: NNH not calculated, since 95% CI for RD includes zero.
- Asthenia/fatigue: NNH not calculated, since 95% CI for RD includes zero.
- Dizziness: NNH 7 (5 to 13).
- Flu syndrome: NNH not calculated, since 95% CI for RD includes zero.
- Somnolence: NNH 9 (6 to 33).
- Abnormal thinking: NNH 20 (11 to 100).

All four placebo-controlled trials of gabapentin reported unambiguous data on the percentage of patients in active treatment groups who withdrew because of adverse events. These percentages were 11% for gabapentin 900 mg in RR 4301-00066, 0% for gabapentin 1200 mg in Di Trapani 2000, 17% for gabapentin 1800 mg in RR 995-00085, and 14% for gabapentin 1800 to 2400 mg in RR 995-00074.

DISCUSSION

Summary of main results

Meta-analysis of the studies included in this review provides little evidence that gabapentin, in any dose, is efficacious for the prophylaxis of migraine. In pooled analyses, mean headache frequency was not significantly reduced with gabapentin as compared to placebo (four studies with 351 patients contributed to this analysis). Furthermore, and perhaps of greater clinical relevance (though less informative scientifically), patients were not more likely to have a ≥ 50% reduction in headache frequency with gabapentin (two studies with 235 patients contributed to this analysis). The majority of patients experienced adverse events from gabapentin.

Dose comparisons suggest that gabapentin 2000 mg/day is no more effective than 1200 mg/day.

Statistically significant findings for both efficacy outcomes (headache frequency and responders) from a single trial of the highest gabapentin dose studied (1800 to 2400 mg/day; RR 995-00074; 113 patients) did not change our overall conclusions given that, for both outcomes, (a) findings from the other individual trials, and from the pooled analyses combining all trials, were statistically insignificant; (b) estimates of effect from the pooled analyses were small; and (c) there was little evidence to suggest a dose-response trend in effect.

The only trial of gabapentin enacarbil versus placebo (Silberstein 2013) did not report sufficient data for us to calculate mean differences (MDs) for headache frequency, our preferred outcome measure, and showed no significant difference between any dose studied (1200, 1800, 2400, and 3000 mg/day) and placebo in the proportion of responders.

We identified no studies evaluating pregabalin for migraine prophylaxis, and no studies comparing gabapentin or gabapentin enacarbil to other active interventions.

Overall completeness and applicability of evidence

The main results of this meta-analysis do not harmonise with current practice, where clinicians regularly prescribe gabapentin as a migraine prophylactic intervention (Drugs.com 2013; Mayo Clinic Staff 2011; Pringsheim 2012).

The studies identified were not sufficient to address all of the objectives of the review for two reasons. First, no controlled trials of pregabalin for the prophylaxis of episodic migraine were identified. Therefore, well-designed trials of pregabalin against placebo or other interventions with demonstrable efficacy in the prophylaxis of migraine are desirable. Second, trials comparing gabapentin with active comparators were not found.

Several important issues need to be taken into account in any assessment of the efficacy of a drug for migraine prophylaxis. Diagnostic criteria, baseline headache frequency, washout periods for previous medication, rules for rescue medication, and the statistical power of the comparison were handled very variably in the six included studies. As investigations of the efficacy of various agents become more commonplace, it seems increasingly important that scientists and clinicians are at least aware of the trial guidelines suggested by the International Headache Society (Tfelt-Hansen 2012). Even if these guidelines cannot — for operational or scientific reasons — be adhered to in their entirety, they provide a useful consultative framework at the early stages of trial design.

Quality of the evidence

The identified body of evidence does not support the use of gabapentin in the prophylaxis of episodic migraine in adults, but does not robustly refute it. As usual in the context of clinical trials research, there was considerable heterogeneity in both headline results and general levels of analytic and statistical sophistication. The highest gabapentin dose studied (1800 to 2400 mg/day), evaluated in a single trial (RR 995-00074; 113 patients) demonstrated a small but statistically significant effect for both efficacy outcomes (headache frequency and responders). For reasons described under Summary of main results, this did not change our overall conclusions. It is fair to say that we faced several difficulties in deriving adequate information from the results of some studies. First, means and standard deviations were not always fully reported for each phase of trials. In tandem with this problem, measures of variability were not always adequately described or labelled. Second, patient numbers did not always seem internally consistent. Third, there was considerable variability in how intention-to-treat analyses were performed.

Potential biases in the review process

Of 36 risk of bias items scored for the six studies, the majority of ratings were either 'unclear' (18 (50%)) or 'low' (11 (31%)) (Figure 1). As described in detail above (Risk of bias in included studies), we judged three trials as having a 'high' risk of bias for at least two items, as follows: random sequence generation (Jimenez 2002),

blinding of participants and personnel (RR 4301-00066; Jimenez 2002), incomplete outcome data (RR 4301-00066; Silberstein 2013), and/or selective reporting (Jimenez 2002; Silberstein 2013). A strength of this review is that the methods used for searching and study selection make it highly likely that most relevant trial results in the public domain were identified. As demonstrated in the cases of RR 4301-00066, RR 995-00085, and RR 995-00074, there is nevertheless an obvious risk that the reports of some trials may have been classified as confidential and thus remain unobtainable.

Agreements and disagreements with other studies or reviews

It is remarkable that our analyses would have been biased in favour of gabapentin had it not been for the inclusion of previously confidential research reports which, after several years, became available in the public domain by virtue of being entered into evidence in a legal proceeding. The overall conclusion in this review, that available data provide little evidence that gabapentin, in any dose, is efficacious for preventing attacks in adult patients with migraine, is in line with the conclusions drawn by the EFNS (Evers 2009) and the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society (Silberstein 2012) but not with those reached by the Canadian Headache Society Prophylactic Guidelines Development Group (Pringsheim 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence derived from trials of gabapentin suggests that it has little or no beneficial effect in migraine prophylaxis while generating side effects in the majority of patients. It may therefore be advocated that it should not be used in routine clinical practice.

The conclusions in this review cannot be extrapolated to chronic migraine, transformed migraine, or chronic daily headache. None of these conditions was considered for this review, as properly validated definitions are as yet lacking. There is no firm evidence for an effect of pregabalin for the prophylaxis of migraine.

Implications for research

Published research on gabapentin for migraine prophylaxis has misled clinicians for a number of years. Enquiry is needed into the causes of this, and the harms that may have resulted.

While efficacy for high doses of gabapentin has not been ruled out, the evidence for this drug, overall, is not promising and does not lead us to recommend further studies with any degree of priority.

There are no controlled trials of pregabalin in the prophylaxis of migraine. Well-designed studies comparing it to placebo and interventions with proven efficacy in migraine are needed.

In general, we feel that the quality of both methods and reporting is disappointing in this area of investigation. In particular, investigators wishing to report intention-to-treat analyses should carefully consider the recommendations of medical statisticians (eg, Hollis 1999). Future trialists should also be encouraged to follow the recommendations of the International Headache Society (Tfelt-Hansen 2012) with regard to both trial design and reporting of data.

ACKNOWLEDGEMENTS

Professor EP Chronicle, PhD, sadly passed away on 9 February 2007. We wish to acknowledge Professor Chronicle's major contribution and tremendous effort in compiling all statistical analyses and much of the text of the original review on antiepileptics (Chronicle 2004; Mulleners 2008). Without his relentless dedication it would have never seen the light of day.

The protocol for the original review was developed while Dr Chronicle was a Visiting Scholar at the University of California, Berkeley. Dr Sally Hollis, Lancaster University, and Dr Kentaro Hayashi, University of Hawaii at Manoa, provided helpful advice on statistical matters. Several pharmaceutical companies kindly provided information about trials in progress.

We thank Ruth Foxlee, Jane Hayes, and Joanne Abbott for assistance in designing search strategies and running searches; Prof Timothy Steiner for editorial guidance; and Dr Rebecca Gray for editorial assistance and technical support.

Lifting The Burden: the Global Campaign against Headache and the International Headache Society provided financial support for the editorial process (see Sources of support).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Di Trapani 2000

Methods	Prospective, randomised, double-blind, parallel-group trial. 1-month baseline period. Duration of treatment: 4 weeks titration then 8 weeks stable dosage Discontinuation rate: dropout 0% Compliance (adherence) data: no compliance data reported Rule for use of acute medication: analgesics were permitted Methodological quality score: 3
Participants	Inclusion: IHS migraine criteria; migraine frequency of 4 to 7 attacks per month for the previous year. No mixed or combination headaches included Exclusion: secondary headaches were adequately excluded. Neither daily headache nor analgesic overuse headache was adequately excluded. Other exclusions: participants with cardiac, hepatic, or renal disease; pregnancy or reproductive intentions; or who had used migraine prophylactic medication in the last 3 months Setting: single headache clinic Country: Italy

Di Trapani 2000 *(Continued)*

	63 migraine patients participated; 31 with aura and 32 without. 33 females, 30 males; age range 18 to 65. 35 received active treatment and 28 received placebo
Interventions	Gabapentin (12 weeks) versus placebo (12 weeks). Dosage titrated up to 1200 mg/day and maintained for 8 weeks
Outcomes	Number of migraine attacks per month. Self reported attack intensity Time point(s) considered in the review: last (third) month of treatment phase
Notes	Senior author confirmed that statistical variance data were SEMs, not SDs (as supposed in our previous review (Chronicle 2004; Mulleners 2008)), and provided data on headache frequency for combined migraine with and without aura groups Funders of the trial: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation of participants reported as performed but method not described
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was reported as double-blind but method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients withdrew
Selective reporting (reporting bias)	Low risk	Results are given for both efficacy measures

Jimenez 2002

Methods	Prospective, randomised, open-label, parallel-group, dose-comparison trial. Duration of treatment: 1- or 2-week titration, then 16 weeks stable dosage Discontinuation rate: dropout 18% over entire period of study Compliance (adherence) data: method of assessing compliance not reported Rule for use of acute medication: not reported Methodological quality score: 2
Participants	Inclusion: IHS migraine criteria; migraine frequency of 3 or more per month, 1 month or more since discontinuation of any previous migraine prophylaxis; adequate contraception

Jimenez 2002 *(Continued)*

	Exclusion: secondary, daily, and analgesic abuse headaches were adequately excluded. Other exclusions: lactation; other severe medical illness, history of alcohol or drug abuse, previous treatment with gabapentin, contraindications to gabapentin Setting: multicentre Country: Spain 164 patients recruited. 81% migraine without aura; 19% migraine with aura. 74% females, 26% males; mean age 35 years. Complete case analysis of 135 patients. 95 received 1200 mg/day and 40 received 2000 mg/day
Interventions	Gabapentin 1200 mg/day versus gabapentin 2000 mg/day (16 weeks). Dosage started at 400 mg/day and incremented over 1 week to reach 1200 mg/day or over 2 weeks to reach 2000 mg/day
Outcomes	Headache frequency per month, pain intensity and duration, global satisfaction of the patient Time point(s) considered in the review: last (fourth) month of treatment phase
Notes	Patient numbers in table V do not appear to be internally consistent Funders of the trial: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random allocation of participants reported as performed but method not described. Very unequal numbers of patients in each dosage group unlikely to be achieved by strict randomisation
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No concern among the review authors over incomplete outcome data
Selective reporting (reporting bias)	High risk	Global satisfaction with treatment measured but not reported. AEs are not reported separately for each group

RR 4301-00066

Methods	Prospective, randomised, double-blind, parallel-group trial. The study, which applied a retrospective baseline (3 months), consisted of a 12-week, double-blind treatment period Discontinuation rate: gabapentin 15%, placebo 16% Compliance (adherence) data: no compliance (adherence) data reported

RR 4301-00066 *(Continued)*

	Rule for use of acute medication: analgesics were allowed for acute treatment but no more than 20 tablets per month Methodological quality score: 4
Participants	Inclusion: migraine without aura according to the Ad Hoc criteria (Ad Hoc Cttee 1962); therapy-resistant (not adequately defined) to standard migraine treatment; migraine frequency minimum 8 episodes per month for the primary study centre and minimum 2 episodes per month for the other study centres. Above 18 years of age. Females of child-bearing potential must utilise an adequate method of contraception Exclusion: chronic daily headache or medication overuse not excluded. Unclear if other secondary headaches were adequately excluded. Other exclusion: use of prophylactic intervention; pregnant or nursing females; severe liver or kidney insufficiency; Parkinson's disease; severe progressive accompanying diseases, eg, diabetes Setting: 5 centres Country: Austria (4 centres) and (West) Germany (1 centre) The SES included all randomised patients: 89; all had migraine without aura; 21/89 also had migraine with aura; 68 were females and 21 males; mean age in gabapentin group 42 (range 20 to 68); mean age in placebo group 42 (range 23 to 68). 46 allocated to receive gabapentin and 43 allocated to receive placebo. The efficacy evaluable population comprised 53 participants. Among them, the proportion with migraine with aura is not reported; 42 were females and 11 males; mean age in gabapentin group 43 (range 20 to 68); mean age in placebo group 40 (range 24 to 59). 22 allocated to gabapentin and 31 to placebo
Interventions	Gabapentin 900 mg/day versus placebo (12 weeks). No information on titration. Capsules of gabapentin (300 mg) or placebo were given 3 times a day
Outcomes	Migraine attack frequency calculated on a 28-day basis. Response ratio defined as difference in attack frequency from baseline to treatment period divided by the sum of attacks during baseline and treatment. Subjective evaluation of improvement of migraine. Duration of attacks (hours) under treatment and the percent reduction in duration relative to baseline. Average pain. Maximal pain during attacks. Change in patients with aura symptoms. The relation between response ratio and dose per kilogram body weight. AEs Time point(s) considered in the review: entire 12-week treatment phase
Notes	Since the baseline was retrospective, change scores from baseline were excluded from the analyses of the present review. This report reveals essential limitations in design and conduct of the study. There are differences between the original protocol (appendix) and the study protocol that is discussed in the main body of the report. Initially it was intended that dropouts (eg, for lack of efficacy) would be replaced with newly randomised subjects, but this does not appear in the final description. Also, all centres were initially to include migraineurs with at least 8 attacks per month, but it is clear that sometime during the conduct of the study this criterion was relaxed to at least 2 attacks per month for most centres. This implies that the design may have changed during the execution of the study. This may have influenced outcomes Funders of the trial: Goedecke AG – Research and Development, Freiburg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation per centre in permuted blocks of 10. No information found on method used for sequence generation
Allocation concealment (selection bias)	Unclear risk	No information

RR 4301-00066 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Both participants and clinicians were blinded. Medications were given as identical capsules distributed in bottles. Bottle labels contained medication number only. It is not specified how subject number was linked to medication number on bottle. Given that the number of gabapentin subjects erroneously receiving other prophylaxis was nearly 3 times higher in the gabapentin group than in the placebo group, it is likely that the blinding was inadequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of protocol violators due to the initiation or continuation of other prophylactics (19 of those allocated to gabapentin; 7 of those allocated to placebo). It is not clear whether the majority initiated other prophylaxis prior to or after randomisation, the higher efficacy means in the gabapentin ITT population (with violators) compared to efficacy population (without violators) suggest that a significant number may have been initiated after randomisation, possibly because of lack of efficacy. Only the data for the smaller efficacy population are included in this review
Selective reporting (reporting bias)	Unclear risk	The research report was never published and results would have remained unobtainable had it not been for the discovery process in a legal case. The response ratio measure was not mentioned in the original protocol (appendix A.2)

RR 995-00074

Methods	Prospective, 2:1 randomised, double-blind, parallel-group trial. 3-week washout period for previous migraine prophylactic medication. 4-week single-blind, placebo-only baseline period. Duration of treatment: 4 weeks titration, then 8 weeks stable dosage Discontinuation rate: dropout 24.5% for active treatment; 20.0% for placebo Compliance (adherence) data: no compliance data reported Rule for use of acute medication: not explicitly reported, but see notes Methodological quality score: 5
Participants	Inclusion: IHS migraine criteria; migraine frequency of 3 to 8 attacks per month for the previous 3 months; no more than 2 previous migraine prophylactic medications. Mixed headaches were included if tension-type headache attacks occurred on 10 or fewer days per month; subgroups cannot be distinguished Exclusion: secondary headaches, daily headaches, and analgesic overuse headache were adequately excluded. Other exclusions: migraine aura without headache, cluster headache, significant CNS disorder, other serious medical or psychological problems, confounding medication Setting: multicentre Country: 7 sites in the USA Of 145 randomised patients (gabapentin 99; placebo 46), 143 received study medication and comprise the SES. 61 of the SES had migraine with aura; 116 were females and 27 males; mean age 39.9 ± 11.3 (range 16 to 71). 98 received active treatment and 45 received placebo. Demographic data for mITT population (77 active; 36 placebo): 50 with aura and 63 without, 92 females and 21 males; mean age 39.9 ± 11.2 (range 16 to 67)

RR 995-00074 *(Continued)*

Interventions	Gabapentin (12 weeks) versus placebo (12 weeks). Dosage titrated up to 1800 to 2400 mg/day and maintained for 8 weeks. We estimate the proportion of patients on 1800 mg versus 2400 mg as 19% (15/78)
Outcomes	Number of migraine attacks per 28 days. Number of migraine days per 28 days. Treatment success. Peak intensity. Attack duration. Functional ability at peak intensity. Aura severity Time point(s) considered in the review: last (third) month of treatment phase
Notes	Ergotamine use up to 2 days per week permitted. NSAIDs, analgesics, benzodiazepines, cyproheptadine, baclofen, SSRIs up to 3 days per week permitted. mITT does not conform to recent recommendations Funders of the trial: Warner-Lambert Company, New Jersey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule, 2:1 ratio
Allocation concealment (selection bias)	Low risk	Each investigator was provided with "blinded" medication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules matched active treatment. During the double-blind phase, investigators, patients, study monitors, and observers were blinded to codes until after the clinical database was locked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No concerns over incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The research report was never published and results would have remained unobtainable had it not been for the discovery process in a legal case

RR 995-00085

Methods	Prospective, randomised, double-blind, parallel-group trial. The 16-week study consisted of a 4-week, single-blind baseline period and a 12-week, double-blind treatment period (divided into a 4-week titration period and an 8-week stable dosing period (the first 4 weeks called Stabilization Period 1 and the second 4 weeks called Stabilization Period 2)) Discontinuation rate: gabapentin 25%, placebo 24% Compliance (adherence) data: compliance was to be measured by counting unused medication and confirming lack of gabapentin in blood drawn from placebo group, but results not summarised in the research report Rule for use of acute medication: symptomatic medications (eg, aspirin, acetaminophen, NSAIDs, tramadol, codeine and codeine derivatives, dihydroergotamine, and ergotamine (< 10 mg/week or ≤ 5 mg/day), sumatriptan, Midrin, antiemetics) were permitted on an "as needed" basis for treatment of individual headaches and were to have been taken 1 hour following initial onset of an attack. These med-

RR 995-00085 *(Continued)*

	ications were to have been taken for less than 3 days each week on average. Narcotics were not to have been used as a first-line treatment Methodological quality score: 4
Participants	Inclusion: migraine with or without aura according to IHS criteria; migraine frequency 3 to 8 episodes per month for each of the 3 months prior to screening and during the 4-week baseline period; history of migraine at least 6 months prior to screening. Ages 16 to 75. Other inclusion criteria: capability of compliance and ability to understand and follow the instructions of the investigator; understanding and capability of completing the study diaries as described in the protocol; informed consent obtained from the patient or legal guardian Exclusion: chronic daily headache or TTH occurring > 10 days/month, medication overuse headache and other secondary headaches were adequately excluded. Other exclusions: if sexually active, female patients must have been practicing a reliable method of contraception and must have had a negative serum pregnancy test; female patients who were using oral contraceptives were to have been using the same product for at least 3 months prior to study entry; previously untreated for migraine prophylaxis or having failed an adequate trial (eg, at least 1 month of treatment at a full therapeutic dose) on no more than 2 prophylactic anti-migraine medications; pregnant or nursing; having received prophylactic anti-migraine medication for a period equal to or greater than 5 half-lives of that medication before entering the baseline phase; previous treatment with gabapentin; migraine aura without headache only; serious neurological, psychiatric, or other medical disorder Setting: 11 centres Country: USA Among the 157 randomised patients (gabapentin 102; placebo 55), 150 received study medication and comprise the SES. Of the SES, 57 had migraine with aura and 93 migraine without aura; 123 were females and 27 males; mean age 39.1 ± 11.0; age range 16 to 64. 95 received gabapentin and 55 received placebo. mITT analysis of 122 patients: 48 had migraine with aura; 97 were females and 25 males; mean age 39.2 ± 11.0 (range 16 to 64). 76 received gabapentin and 45 received placebo
Interventions	Gabapentin 1800 mg/day versus placebo (12 weeks). Gabapentin 300 mg capsule starting with 1 at night-time and then titrated up to 1800 mg/day divided into BID dosing during a 4-week period. Thereafter stable dosing. 94/95 SES patients treated with active treatment received 1800 mg/day as the final stable dose. Placebo capsules were titrated in the same manner as active treatment
Outcomes	Headache frequency per 28 days. Proportion of responders (≥ 50% reduction in migraine attacks). Average severity at peak intensity. Average duration of migraine headache. Average functional ability at the time of peak intensity. Aura severity. Number of days per 4 weeks with a migraine headache. SF-36 quality of life. AEs. Vital signs. Physical examinations. Laboratory assessments Time point(s) considered in the review: Stabilization Period 2, ie, third month of treatment
Notes	Funders of the trial: Warner-Lambert Company, New Jersey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in a 2:1 ratio was performed by the Clinical Pharmaceutical Operations (CPO) Department of Parke-Davis. No information on method used for randomisation found
Allocation concealment (selection bias)	Low risk	Blinded medication provided by CPO or other designated facility based on the randomisation code
Blinding of participants and personnel (performance bias)	Low risk	Clinicians and patients were blinded. Gabapentin and placebo were provided as capsules identical in size and colour by Parke-Davis, packaged in patient-specific bottles and shipped to investigators

RR 995-00085 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No concerns over incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	The research report was never published and results would have remained unobtainable had it not been for the discovery process in a legal case

Silberstein 2013

Methods	Prospective, randomised, double-blind, parallel-group trial. The 30-week study consisted of a 2-week screening period, a 6-week baseline period, a 5-week flexible titration period, a 12-week maintenance period, a 3-week tapering out period, and a 2-week post-treatment AE monitoring period Discontinuation rate: GEn 1200 mg 27%, GEn 1800 mg 34%, GEn 2400 mg 28%, GEn 3000 mg 40%, placebo 26% Compliance (adherence) data: no compliance (adherence) data reported Rule for use of acute medication: use of acute migraine medication was permitted for breakthrough migraine attacks Methodological quality score: 4
Participants	Inclusion: migraine with or without aura according to ICHD-II; migraine frequency ≥ 3 attacks and ≥ 4 calendar days per month during each of the 3 months prior to screening and during baseline; migraines consistent in incidence and severity over time; history of migraine at least 1 year prior to screening; onset of migraine before age 50. Ages 18 and above. Other inclusion criteria: written informed consent Exclusion: chronic daily headache (≥ 15 migraine or non-migraine headache days per month); history of ergotamine, triptan, opioid, or combination analgesic intake ≥ 10 days per month or simple analgesic intake ≥ 15 days per month, for ≥ 3 months. Secondary headaches were adequately excluded. Other exclusions: pregnancy; child-bearing potential and inadequate contraception; unable to discontinue beta-blockers, TCAs, Ca-blockers, antiepileptic drugs, bupropion, SNRIs during screening and study duration (fluoxetine, riboflavin, Mg and feverfew allowed); previous use of gabapentin or pregabalin for migraine prophylaxis; lack of efficacy of ≥ 2 trials of migraine prophylaxis for ≥ 8 weeks; uncontrolled hypertension (> 160 mmHg systolic or > 90 mmHg diastolic in sitting position) Setting: 51 centres Countries: USA and Canada ITT analysis of 523 patients. No information on how many had migraine with aura; 429 were females and 94 males; mean ages: GEn 1200 mg 39.4 ± 9.74, GEn 1800 mg 37.7 ± 11.75; GEn 2400 mg 39.0 ± 12.04; GEn 3000 mg 39.1 ± 11.78, placebo 41.1 ± 11.72; allocation of randomised subjects: GEn 1200 mg 67; GEn 1800 mg 134; GEn 2400 mg 134; GEn 3000 mg 62, placebo 129
Interventions	Gabapentin enacarbil (GEn) 1200 mg/day versus GEn 1800 mg/day versus GEn 2400 mg/day versus GEn 3000 mg/day versus placebo (20 weeks). GEn given BID, orally and titrated within 5 weeks to target dose or the maximum tolerated dose
Outcomes	Migraine attacks per 4 weeks. Migraine days (calendar days with any occurrence of migraine head pain ≥ 30 min duration). Migraine headache periods (24-hour segment with migraine). Proportion with ≥ 50% reduction in migraine attacks, migraine days, migraine periods. Attack duration. Peak migraine pain severity. Acute migraine medication use. Occurrence of aura, nausea, vomiting, photophobia, phonophobia. AEs

Silberstein 2013 *(Continued)*	
	Time point(s) considered in the review: last (third) month of maintenance period
Notes	Funder of the trial: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blocks of randomisation codes were assigned to each centre. Information on block size and code generation not provided. Randomisation ratio: 2 placebo : 1 GEn 1200 mg : 2 GEn 1800 mg : 2 GEn 2400 mg : 1 GEn 3000 mg
Allocation concealment (selection bias)	Low risk	Interactive voice recognition system (IVRS)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is assumed from the term 'double-blind' that participants and clinicians were blinded. No information on method used. Potential unblinding by AEs (notably dizziness)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Subjects have been randomised despite missing baseline values. Missing values in secondary outcomes not accounted for
Selective reporting (reporting bias)	High risk	Within-group changes (with standard deviations) from baseline in mean migraine frequencies during the double-blind period lacking. Only differences in changes (with 95% CIs) from placebo given in publication. Supplementary information requested corresponding author, but no reply

Abbreviations: AE = adverse event; BID = twice a day; CI = confidence interval; CNS = central nervous system; GEn = gabapentin enacarbil; ICHD-II = International Classification of Headache Disorders, 2nd Edition; IHS = International Headache Society; ITT = intention-to-treat; mITT = modified intention-to-treat; NSAIDs = non-steroidal anti-inflammatory drugs; SD = standard deviation; SEM = standard error of the mean; SES = safety-evaluable subjects; SNRIs = serotonin–norepinephrine reuptake inhibitors; SSRIs = selective serotonin re-uptake inhibitors; TCA = tricyclic antidepressant; TTH = tension-type headache

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cutrer 2001	Basic science paper
Jimenez 1999	Abstract only
Mathew 2001	Post hoc subgroup analysis of RR 995-00074 (included). "Modified intention-to-treat" (mITT) population described in Mathew 2001 (n = 87; gabapentin 56, placebo 31) is smaller and more select than the mITT population described in RR 995-00074 (n = 113; gabapentin 77, placebo 36). This is due to the exclusion in Mathew 2001 of participants who did not maintain a stable dose of 2400 mg/day of study medication during the last (third) month of the treatment phase. By focusing on this narrower population, Mathew 2001 overstates the efficacy of gabapentin when compared with the results as reported in RR 995-00074 (McCrory 2008; Saris 2010; Vedula 2009)
Merren 1998	Reports case studies only

Study	Reason for exclusion
Spira 2003	Reports data on chronic daily headache only
Wessely 1987	Extended abstract only; insufficient information provided. Close similarities in the design of the trial and the fact that there are several names in common between the authors of this abstract and the outside investigators listed in RR 4301-00066 lead us to conclude that this abstract reports an interim analysis of RR 4301-00066 (included). Some differences between this abstract and RR 4301-00066 in the results and numbers of patients are likely explained by this abstract being an interim report (before completion) while RR 4301-00066 represents a final report (after completion)

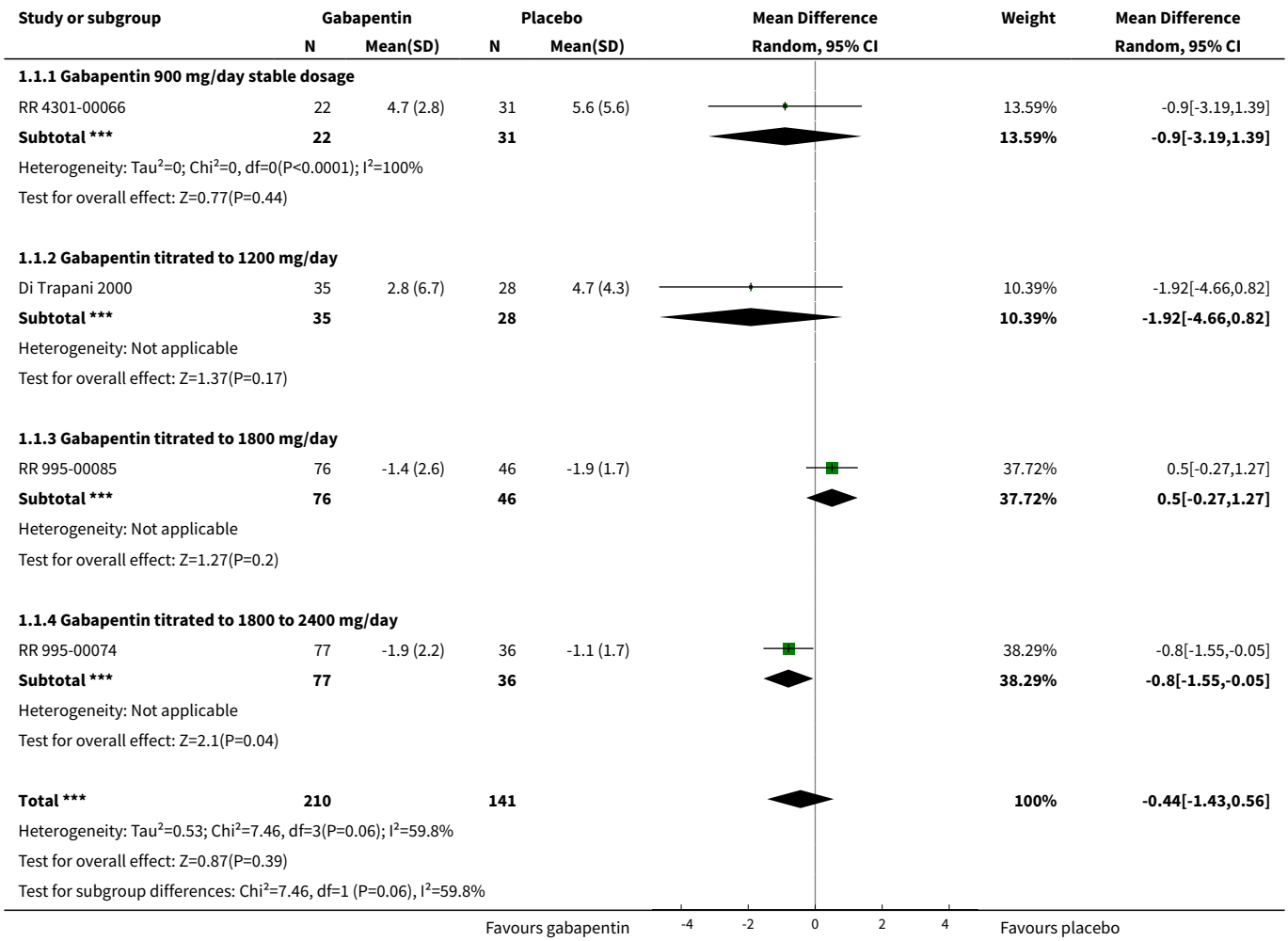
DATA AND ANALYSES

Comparison 1. Gabapentin versus placebo

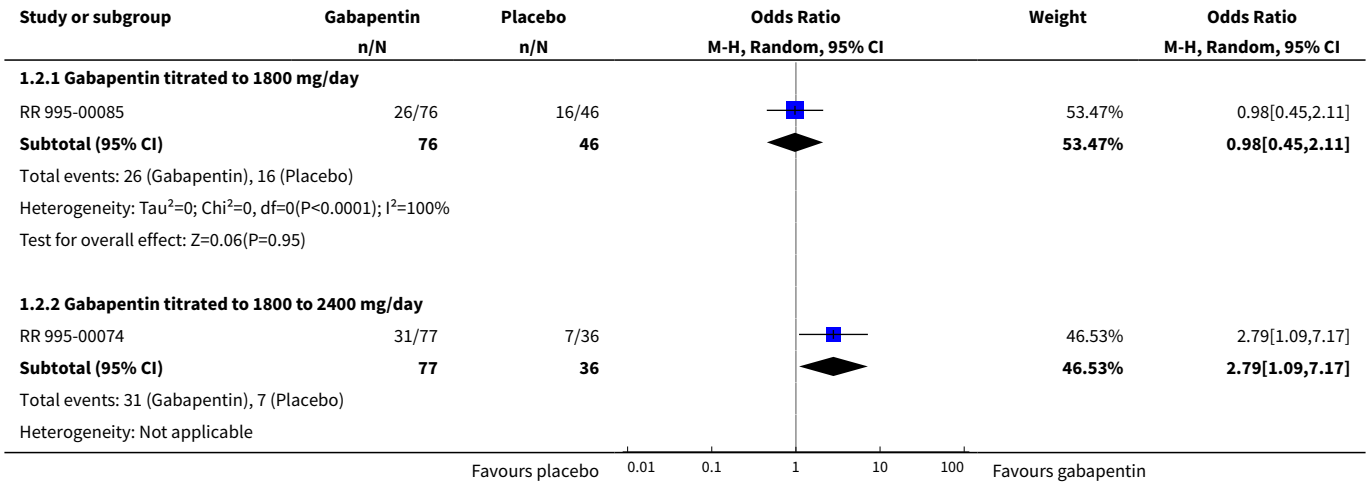
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache frequency (change from baseline to post-treatment, or post-treatment alone)	4	351	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.43, 0.56]
1.1 Gabapentin 900 mg/day stable dosage	1	53	Mean Difference (IV, Random, 95% CI)	-0.90 [-3.19, 1.39]
1.2 Gabapentin titrated to 1200 mg/day	1	63	Mean Difference (IV, Random, 95% CI)	-1.92 [-4.66, 0.82]
1.3 Gabapentin titrated to 1800 mg/day	1	122	Mean Difference (IV, Random, 95% CI)	0.5 [-0.27, 1.27]
1.4 Gabapentin titrated to 1800 to 2400 mg/day	1	113	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.55, -0.05]
2 Responders (patients with ≥ 50% reduction in headache frequency)	2	235	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.57, 4.46]
2.1 Gabapentin titrated to 1800 mg/day	1	122	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.45, 2.11]
2.2 Gabapentin titrated to 1800 to 2400 mg/day	1	113	Odds Ratio (M-H, Random, 95% CI)	2.79 [1.09, 7.17]
3 Any adverse event	3	382	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.04, 0.14]
3.1 Gabapentin 900 mg/day stable dosing	1	89	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.14, 0.20]
3.2 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	0.06 [-0.09, 0.22]

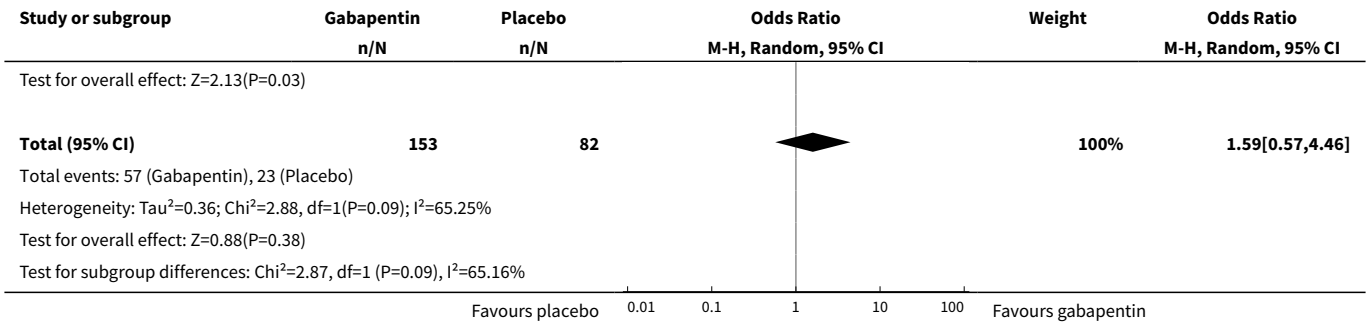
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Gabapentin titrated to 1800 to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.09, 0.19]
4 Asthenia/fatigue	3	382	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.08, 0.03]
4.1 Gabapentin 900 mg/day stable dosing	1	89	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.10, 0.05]
4.2 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.12, 0.07]
4.3 Gabapentin titrated to 1800 to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.20, 0.11]
5 Dizziness	3	382	Risk Difference (M-H, Random, 95% CI)	0.15 [0.08, 0.22]
5.1 Gabapentin 900 mg/day stable dosing	1	89	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.03, 0.20]
5.2 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	0.21 [0.11, 0.31]
5.3 Gabapentin titrated to 1800 to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	0.14 [0.02, 0.27]
6 Flu syndrome	2	293	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.03, 0.08]
6.1 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.03, 0.11]
6.2 Gabapentin titrated to 1800 to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.10, 0.10]
7 Somnolence	2	293	Risk Difference (M-H, Random, 95% CI)	0.11 [0.03, 0.18]
7.1 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.00, 0.19]
7.2 Gabapentin titrated to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	0.13 [0.01, 0.26]
8 Abnormal thinking	3	382	Risk Difference (M-H, Random, 95% CI)	0.05 [0.01, 0.09]
8.1 Gabapentin 900 mg/day stable dosing	1	89	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.03, 0.11]
8.2 Gabapentin titrated to 1800 mg/day	1	150	Risk Difference (M-H, Random, 95% CI)	0.07 [0.01, 0.13]
8.3 Gabapentin titrated to 1800 to 2400 mg/day	1	143	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.03, 0.09]

Analysis 1.1. Comparison 1 Gabapentin versus placebo, Outcome 1 Headache frequency (change from baseline to post-treatment, or post-treatment alone).

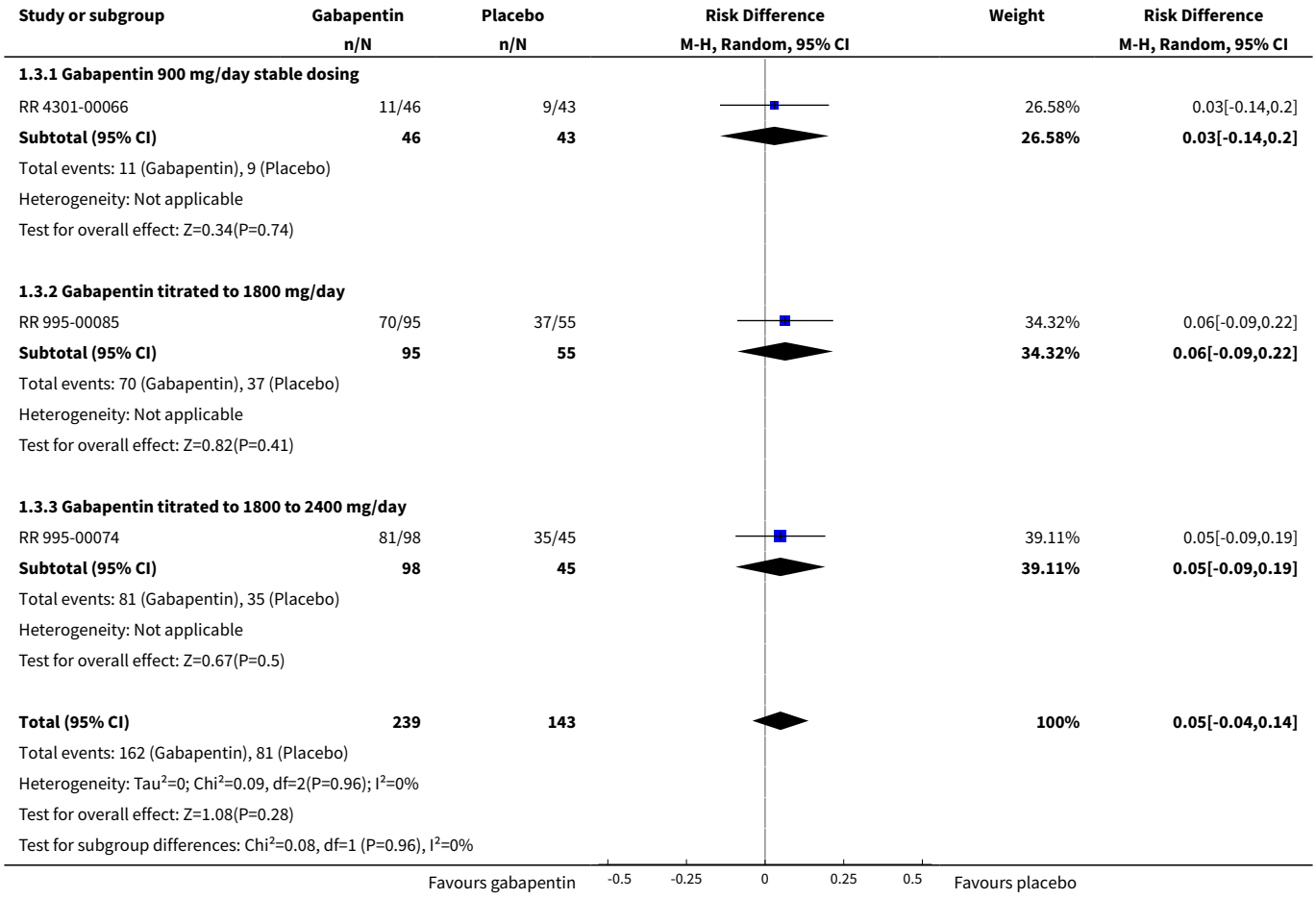


Analysis 1.2. Comparison 1 Gabapentin versus placebo, Outcome 2 Responders (patients with ≥ 50% reduction in headache frequency).

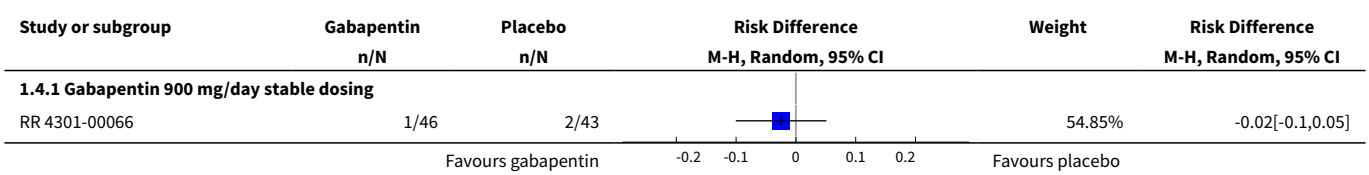


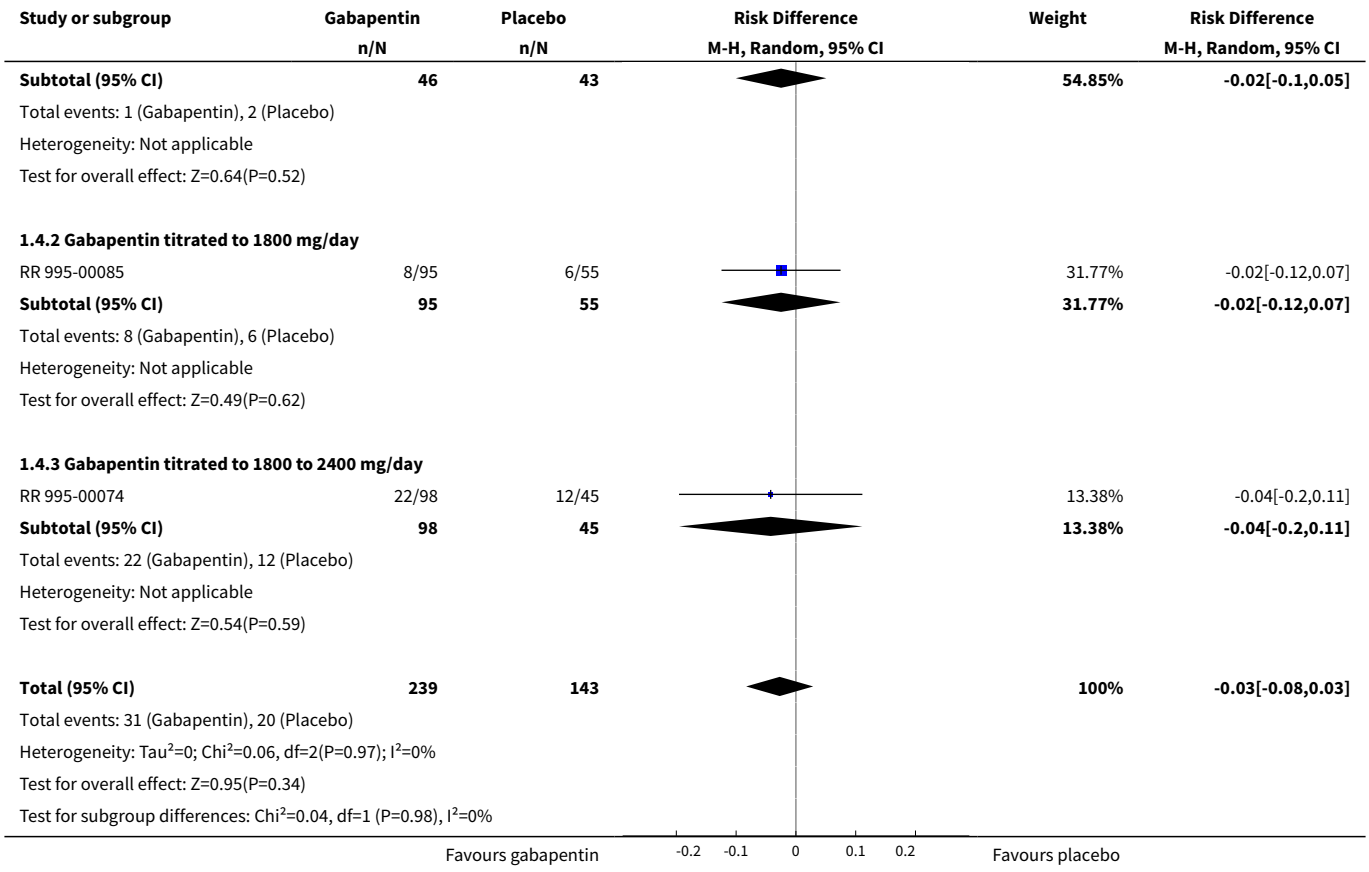


Analysis 1.3. Comparison 1 Gabapentin versus placebo, Outcome 3 Any adverse event.

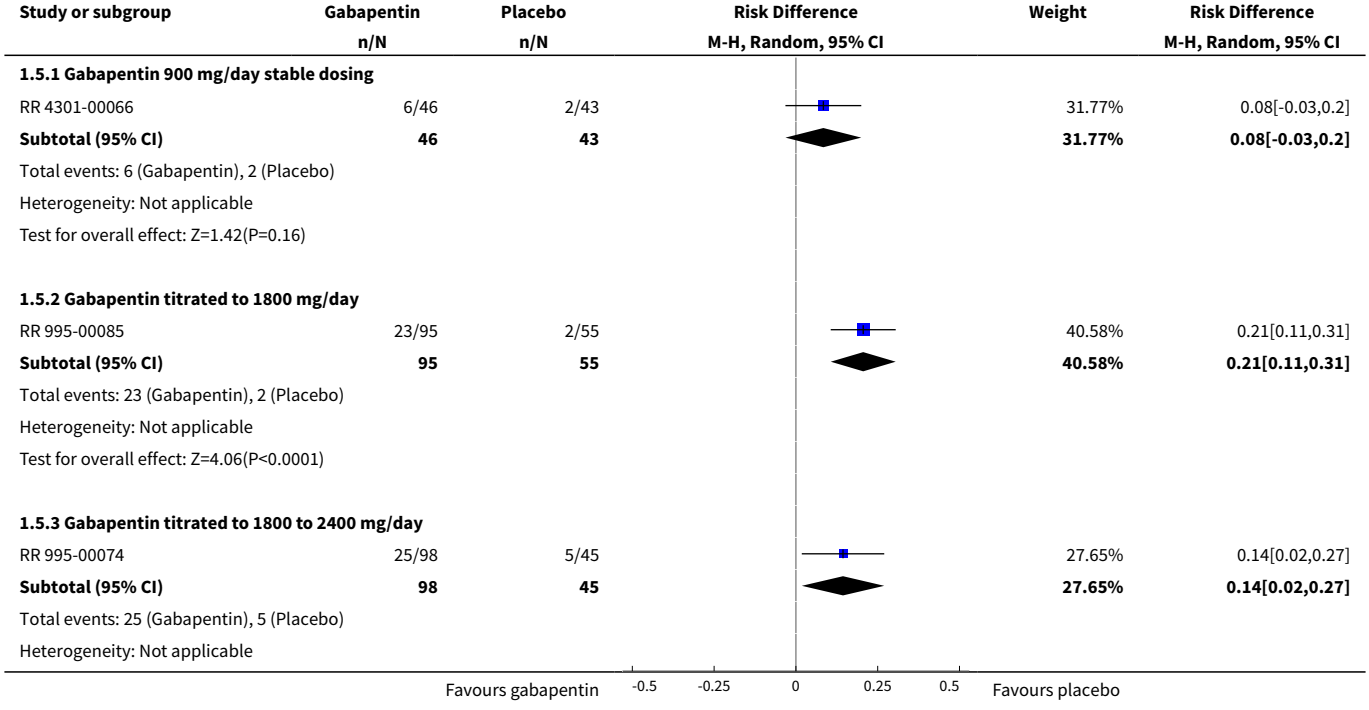


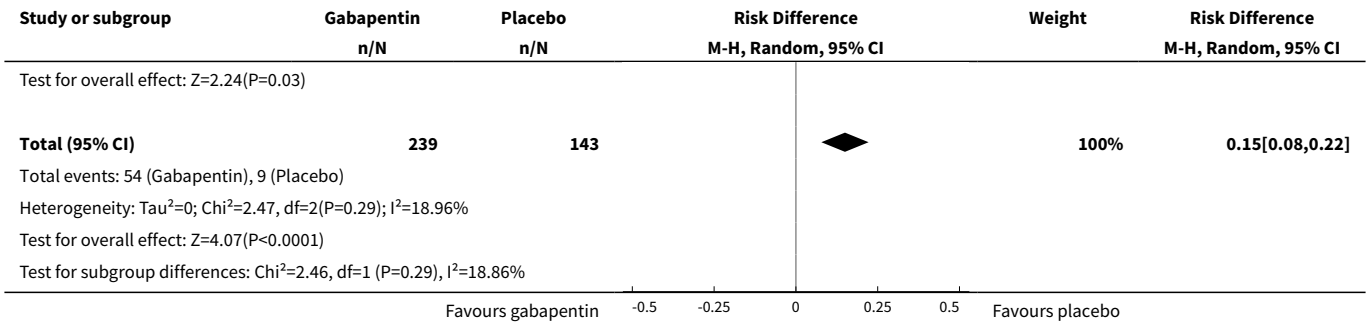
Analysis 1.4. Comparison 1 Gabapentin versus placebo, Outcome 4 Asthenia/fatigue.



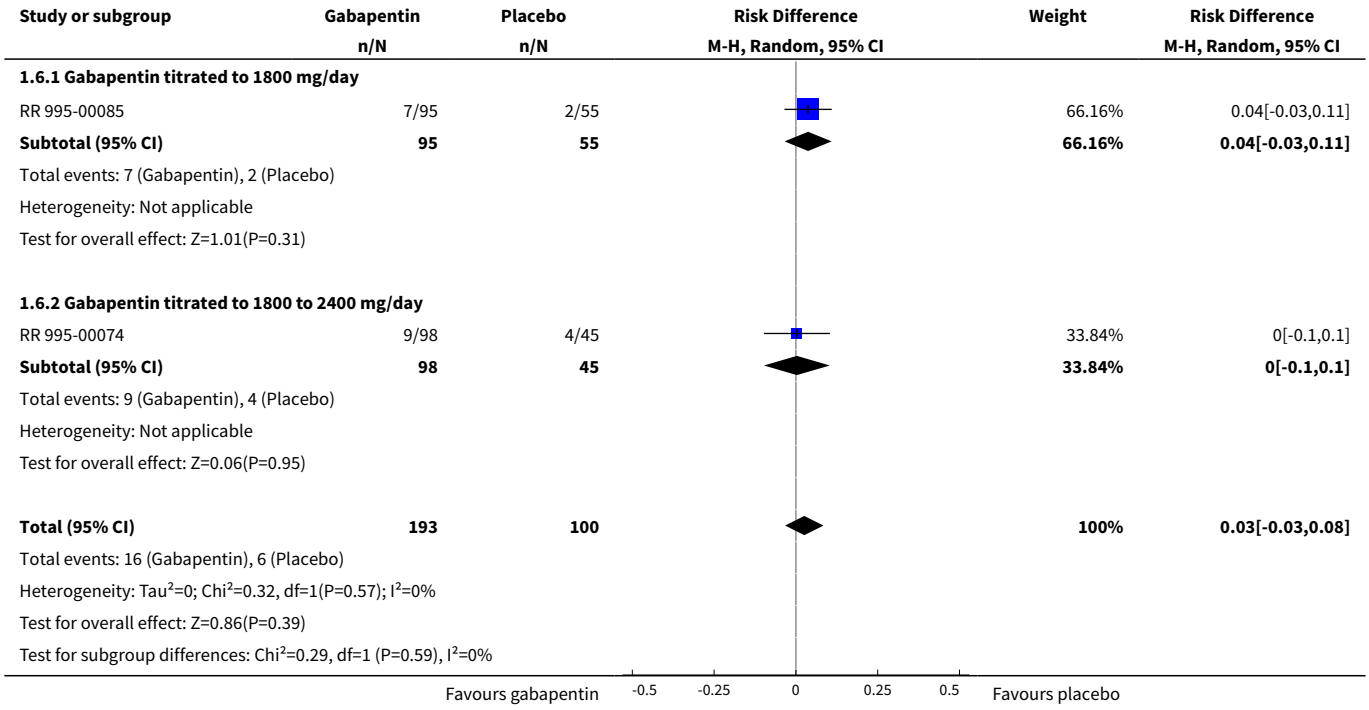


Analysis 1.5. Comparison 1 Gabapentin versus placebo, Outcome 5 Dizziness.

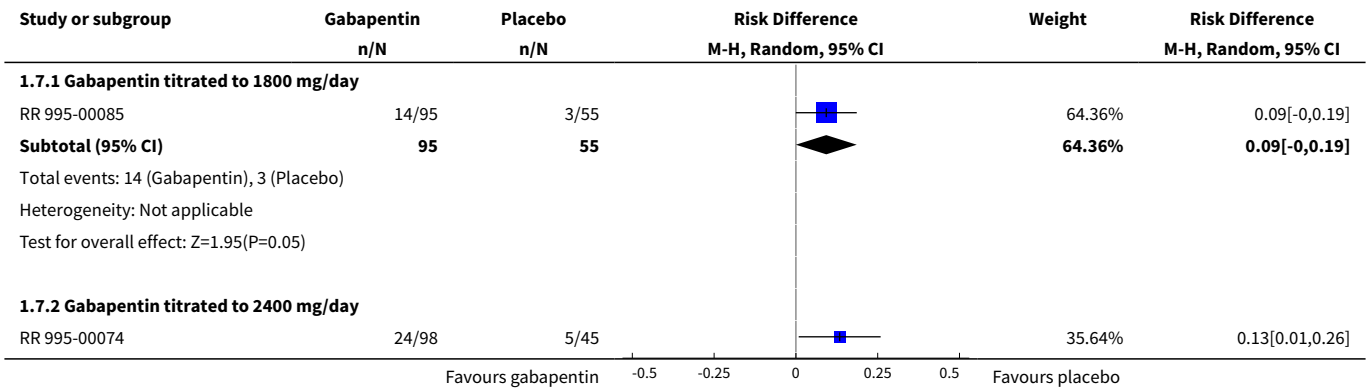


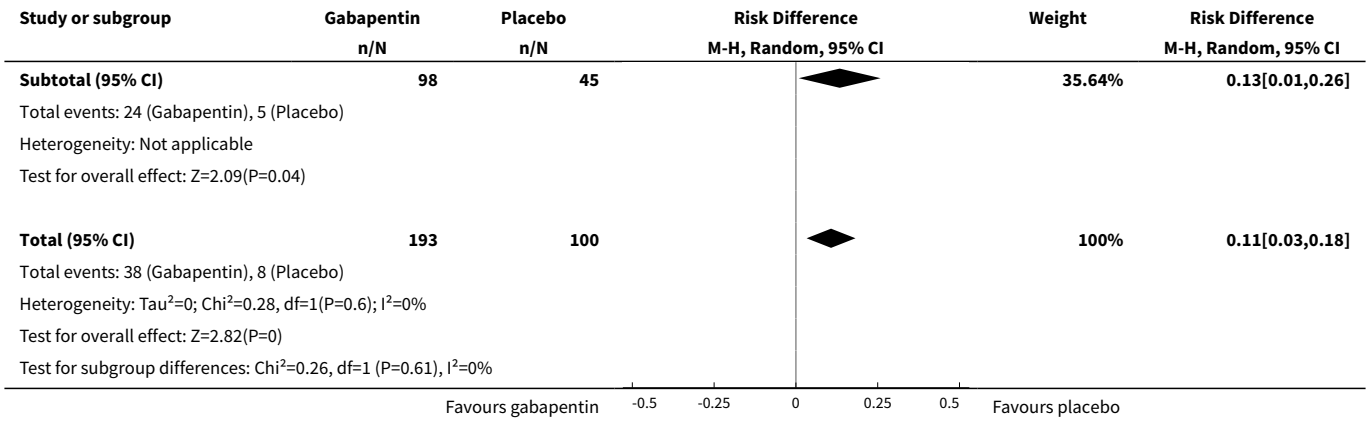


Analysis 1.6. Comparison 1 Gabapentin versus placebo, Outcome 6 Flu syndrome.

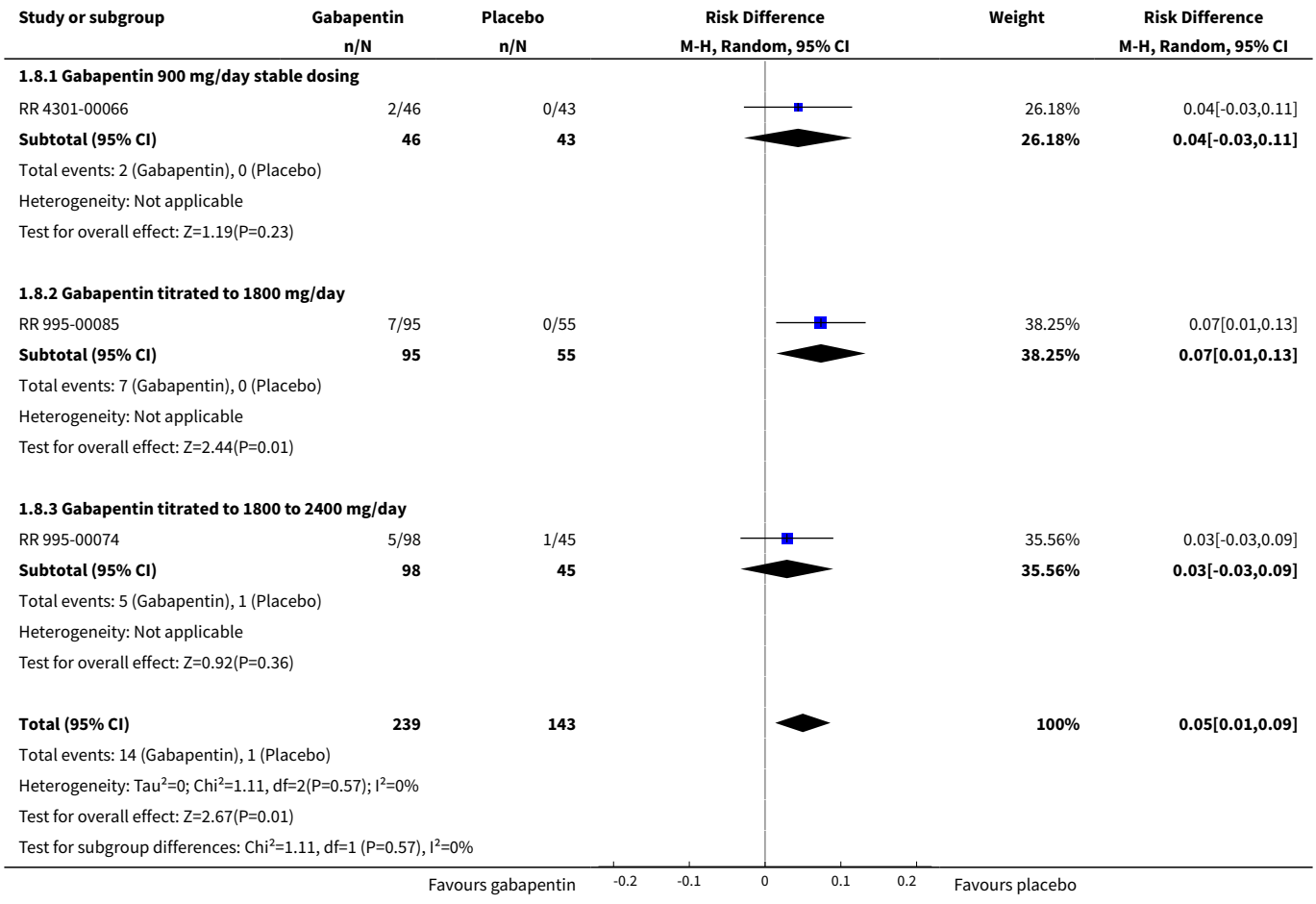


Analysis 1.7. Comparison 1 Gabapentin versus placebo, Outcome 7 Somnolence.





Analysis 1.8. Comparison 1 Gabapentin versus placebo, Outcome 8 Abnormal thinking.

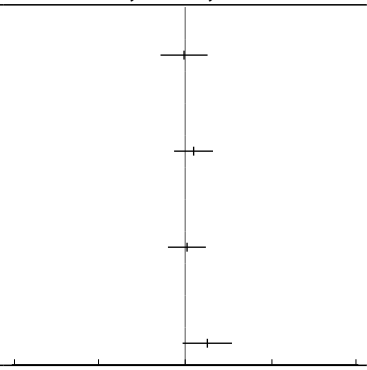


Comparison 2. Gabapentin enacarbil (GEn) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Responders (patients with ≥ 50% reduction in headache frequency)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 GEn titrated to 1200 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 GEn titrated to 1800 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 GEn titrated to 2400 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 GEn titrated to 3000 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Gabapentin enacarbil (GEn) versus placebo, Outcome 1 Responders (patients with ≥ 50% reduction in headache frequency).

Study or subgroup	GEn n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
2.1.1 GEn titrated to 1200 mg/day				
Silberstein 2013	31/59	64/120		0.97[0.52,1.81]
2.1.2 GEn titrated to 1800 mg/day				
Silberstein 2013	67/114	64/120		1.25[0.74,2.09]
2.1.3 GEn titrated to 2400 mg/day				
Silberstein 2013	67/123	64/120		1.05[0.63,1.73]
2.1.4 GEn titrated to 3000 mg/day				
Silberstein 2013	39/58	64/120		1.8[0.93,3.46]

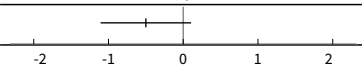


Comparison 3. Gabapentin dose comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache frequency (post-treatment)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Responders (patients with ≥ 50% reduction in headache frequency)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Gabapentin dose comparisons, Outcome 1 Headache frequency (post-treatment).

Study or subgroup	Gabapentin 2000 mg		Gabapentin 1200 mg		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Jimenez 2002	40	1.6 (1.4)	95	2.1 (2.1)		-0.5[-1.11,0.11]



Analysis 3.2. Comparison 3 Gabapentin dose comparisons, Outcome 2 Responders (patients with ≥ 50% reduction in headache frequency).

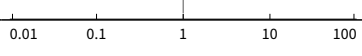
Study or subgroup	Gabapentin 2000 mg	Gabapentin 1200 mg	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Jimenez 2002	25/40	62/95		0.89[0.41,1.91]

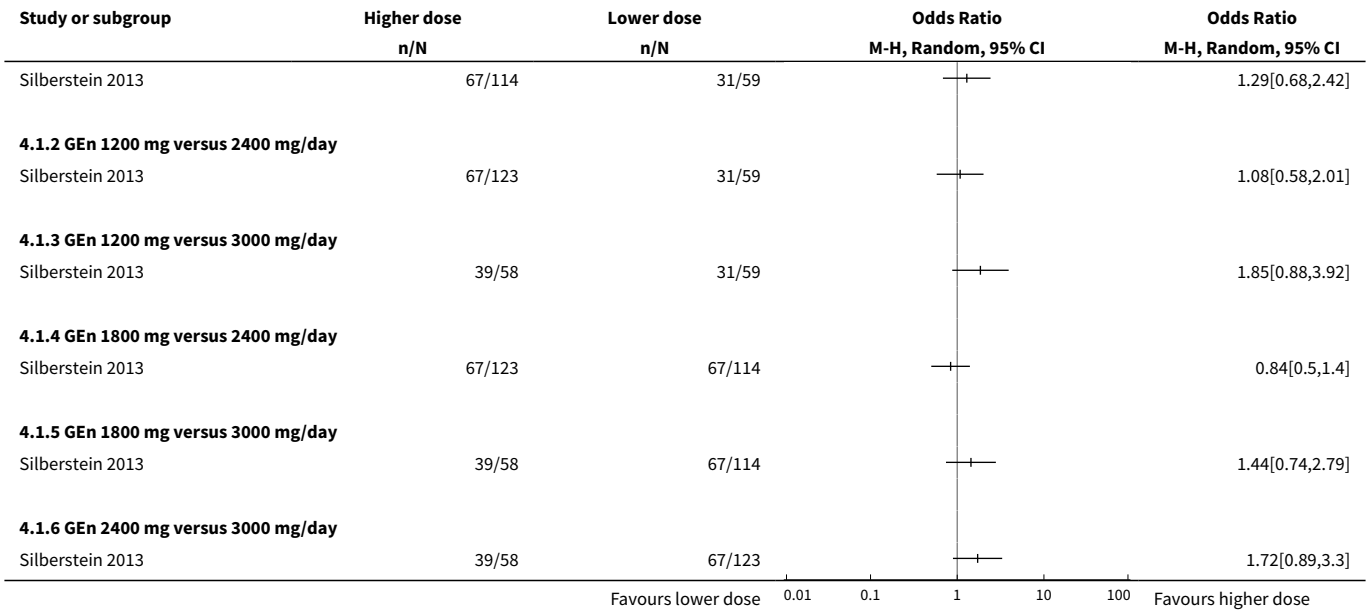
Comparison 4. Gabapentin enacarbil (GEn) dose comparisons

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Responders (patients with ≥ 50% reduction in headache frequency)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 GEn 1200 mg versus 1800 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 GEn 1200 mg versus 2400 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 GEn 1200 mg versus 3000 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 GEn 1800 mg versus 2400 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 GEn 1800 mg versus 3000 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 GEn 2400 mg versus 3000 mg/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Gabapentin enacarbil (GEn) dose comparisons, Outcome 1 Responders (patients with ≥ 50% reduction in headache frequency).

Study or subgroup	Higher dose	Lower dose	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
4.1.1 GEn 1200 mg versus 1800 mg/day				





ADDITIONAL TABLES

Table 1. Numbers (percentages) of adverse events (AEs) in placebo-controlled studies of gabapentin

Study	Type of AE*	Active treatment	Control
RR 4301-00066		**Gabapentin 900 mg** (n = 46)	**Placebo** (n = 43)
	Any AE	11 (24)	9 (21)
	Dizziness	6 (13)	2 (5)
	Nausea/vomiting	4 (9)	3 (7)
	Fatigue	1 (2)	2 (5)
	Withdrawal due to AE	5 (11)	1 (2)
Di Trapani 2000		**Gabapentin 1200 mg** (n = 35)	**Placebo** (n = 28)
	Somnolence		
	Dizziness		
	Tremor	Total of 13 events	Not reported
	Fatigue		
	Ataxia		

Table 1. Numbers (percentages) of adverse events (AEs) in placebo-controlled studies of gabapentin *(Continued)*

	Withdrawal due to AE	0	0

RR 995-00085		**Gabapentin 1800 mg** (n = 95)	**Placebo** (n = 55)
	Any AE	70 (74)	37 (67)
	Dizziness	23 (24)	2 (4)
	Somnolence	14 (15)	3 (5)
	Asthenia	8 (8)	6 (11)
	Flu syndrome	7 (7)	2 (4)
	Abnormal thinking	7 (7)	0
	Back pain	6 (6)	0
	Pharyngitis	5 (5)	1 (2)
	Dry mouth	5 (5)	0
	Pain	4 (4)	4 (7)
	Headache	2 (2)	4 (7)
	Withdrawal due to AE	16 (17)	7 (13)

RR 995-00074		**Gabapentin 2400 mg** (n = 98)	**Placebo** (n = 45)
	Any AE	81 (83)	35 (78)
	Dizziness	25 (26)	5 (11)
	Somnolence	24 (24)	5 (11)
	Asthenia	22 (22)	12 (27)
	Infection	11 (11)	11 (24)
	Flu syndrome	9 (9)	4 (9)
	Sinusitis	8 (8)	3 (7)
	Nausea	6 (6)	4 (9)
	Diarrhoea	6 (6)	2 (4)
	Pain	6 (6)	1 (2)

Table 1. Numbers (percentages) of adverse events (AEs) in placebo-controlled studies of gabapentin *(Continued)*

	Confusion	6 (6)	0
	Flatulence	6 (6)	0
	Abnormal thinking	5 (5)	1 (2)
	Nervousness	5 (5)	0
	Withdrawal due to AE	14 (14)	4 (9)

*For RR 4301-00066, RR 995-00085, and RR 995-00074, only AEs reported by ≥ 5% participants in at least 1 group are included in the table.
Abbreviation: AE = adverse event

Table 2. Numbers (percentages) of adverse events (AEs) in placebo-controlled studies of gabapentin enacarbil (GEn)

Study	Type of AE*	Active treatment				Control
Silberstein 2013		GEn 1200 mg (n = 66)	GEn 1800 mg (n = 134)	GEn 2400 mg (n = 133)	GEn 3000 mg (n = 62)	Placebo (n = 128)
	Any AE	44 (67)	99 (74)	101 (76)	49 (79)	87 (68)
	Dizziness	16 (24)	43 (32)	35 (26)	11 (18)	8 (6)
	Fatigue	10 (15)	12 (9)	14 (11)	3 (5)	9 (7)
	Nausea	3 (5)	15 (11)	12 (9)	6 (10)	12 (9)
	Somnolence	6 (9)	7 (5)	14 (11)	9 (15)	6 (5)
	Weight increase	4 (6)	8 (6)	9 (7)	4 (6)	7 (5)
	Upper respiratory tract infection	4 (6)	4 (3)	9 (7)	5 (8)	9 (7)
	Constipation	4 (6)	7 (5)	8 (6)	5 (8)	3 (2)
	Dry mouth	4 (6)	6 (4)	5 (4)	3 (5)	3 (2)
	Nasopharyngitis	3 (5)	4 (3)	4 (3)	2 (3)	8 (6)
	Diarrhoea	1 (2)	1 (< 1)	7 (5)	1 (2)	8 (6)
	Vomiting	1 (2)	3 (2)	7 (5)	2 (3)	5 (4)
	Influenza	1 (2)	3 (2)	4 (3)	3 (5)	4 (3)
	Insomnia	4 (6)	1 (< 1)	6 (5)	2 (3)	1 (< 1)
	Peripheral edema	4 (6)	1 (< 1)	3 (2)	2 (3)	4 (3)
	Sinusitis	4 (6)	3 (2)	3 (2)	1 (2)	3 (2)

Table 2. Numbers (percentages) of adverse events (AEs) in placebo-controlled studies of gabapentin enacarbil (GEn) *(Continued)*

	Balance disorder	2 (3)	2 (1)	6 (5)	1 (2)	1 (< 1)
	Abdominal pain	2 (3)	2 (1)	3 (2)	3 (5)	1 (< 1)
	Back pain	1 (2)	6 (4)	1 (< 1)	3 (5)	0
	Cough	3 (5)	1 (< 1)	0	0	0
	Withdrawal due to AE	4 (6)	17 (13)	16 (12)	13 (21)	11 (9)

*Only AEs reported by ≥ 5% participants in at least 1 group are included in the table.
Abbreviations: AE = adverse event; GEn = gabapentin enacarbil

APPENDICES

Appendix 1. Search strategies for the previous review

For the identification of studies considered for the original review and the 2007 update (Chronicle 2004; Mulleners 2008), detailed search strategies were developed for each database searched. These were based on the search strategy for PubMed, but revised appropriately for each database. The search strategies combined the subject searches described below with the Cochrane highly sensitive search strategy for RCTs current at the time (Alderson 2004). The subject searches used a combination of controlled vocabulary and free-text terms based on the search strategy for PubMed presented below.

Databases searched were:

- Cochrane Pain, Palliative & Supportive Care Trials Register;
- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2005, Issue 3);
- PubMed 1966 to 31 December 2005;
- EMBASE 1974 to 31 December 2005.

Additional strategies for identifying trials included searching the reference lists of review articles and included studies, searching books related to headache and consulting experts in the field. Two journals, *Headache* and *Cephalalgia*, were handsearched in their entirety, through April 2006.

Detailed descriptions of the subject search strategies used for PubMed, EMBASE, and CENTRAL are given below.

PubMed

Phase 1

#1 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh]) Limits: Humans

Phase 2

#2 HEADACHE Field: MeSH Terms, Limits: Humans
#3 HEADACHE DISORDERS Field: MeSH Terms, Limits: Humans
#4 headache* OR migrain* OR cephalgi* OR cephalalgi* Field: All Fields, Limits: Humans
#5 #2 OR #3 OR #4 Limits: Humans

Phase 3

#6 anticonvulsant* OR antiepileptic* OR acetazolamide OR carbamazepine OR chlormethiazole OR clobazam OR clonazepam OR clorazepate OR diazepam OR divalproex OR ethosuximide OR felbamate OR fosphenytoin OR gabapentin OR lamotrigine OR levetiracetam OR lidocaine OR lignocaine OR lorazepam OR mephobarbital OR methsuximide OR midazolam OR nitrazepam OR oxcarbazepine OR

paraldehyde OR pentobarbital OR phenobarbital OR phenytoin OR primidone OR valproate OR tiagabine OR topiramate OR valproic OR vigabatrin OR zonisamide Field: All Fields, Limits: Humans
#7 #1 AND #5 AND #6

EMBASE

#1 'migraine'/exp AND [embase]/lim
#2 migrain* OR cephalgi* OR cephalalgi* AND [embase]/lim
#3 headache*:ti
#4 #1 OR #2 OR #3
#5 'anticonvulsive agent'/de AND [embase]/lim
#6 anticonvulsant* OR antiepileptic* OR 'acetazolamide'/de OR 'carbamazepine'/de OR 'chlormethiazole'/de OR 'clobazam'/de OR 'clonazepam'/de OR 'clorazepate'/de OR 'diazepam'/de OR 'divalproex'/de OR 'ethosuximide'/de OR 'felbamate'/de OR fosphenytoin OR 'gabapentin'/de OR 'lamotrigine'/de OR 'levetiracetam'/de OR 'lidocaine'/de OR 'lignocaine'/de OR 'lorazepam'/de OR 'mephobarbital'/de OR 'methsuximide'/de OR 'midazolam'/de OR 'nitrazepam'/de OR 'oxcarbazepine'/de OR 'paraldehyde'/de OR 'pentobarbital'/de OR 'phenobarbital'/de OR 'phenytoin'/de OR 'primidone'/de OR 'valproate'/de OR 'tiagabine'/de OR 'topiramate'/de OR valproic OR 'vigabatrin'/de OR 'zonisamide'/de AND [embase]/lim
#7 #5 OR #6
#8 #4 AND #7
#9 ((random*:ti,ab) OR (factorial*:ab,ti) OR (crossover*:ab,ti OR 'cross over':ab,ti OR 'cross over':ab,ti) OR (placebo*:ab,ti) OR ('double blind' OR 'double blind') OR ('single blind':ab,ti OR 'single blind':ab,ti) OR (assign*:ti,ab OR allocat*:ti,ab) OR (volunteer*:ab,ti) OR ('randomized controlled trial'/exp AND [embase]/lim) OR ('single blind procedure'/exp AND [embase]/lim) OR ('double blind procedure'/exp AND [embase]/lim) OR ('crossover procedure'/exp AND [embase]/lim)) NOT ((animal/ OR nonhuman/ OR 'animal'/de AND experiment/ AND [embase]/lim) NOT ((human/ AND [embase]/lim) AND (animal/ OR nonhuman/ OR 'animal'/de AND experiment/ AND [embase]/lim)) AND [embase]/lim) AND [embase]/lim
#10 #8 AND #9

CENTRAL

(migrain* OR headache*) AND (randomized controlled trial OR controlled clinical trial) Field: All Fields

Appendix 2. Search strategies for this update

CENTRAL

#1 MeSH descriptor: [Migraine Disorders] explode all trees
#2 (migrain* or cephalgi* or cephalalgi*)
#3 #1 or #2
#4 MeSH descriptor: [Anticonvulsants] explode all trees
#5 (anticonvulsant* or antiepileptic* or acetazolamide or carbamazepine or chlormethiazole or clobazam or clonazepam or clorazepate or diazepam or divalproex or ethosuximide or felbamate or fosphenytoin or gabapentin or lamotrigine or levetiracetam or lidocaine or lignocaine or lorazepam or mephobarbital or methsuximide or midazolam or nitrazepam or oxcarbazepine or paraldehyde or pentobarbital or phenobarbital or phenytoin or primidone or valproate or tiagabine or topiramate or valproic or vigabatrin or zonisamide or eslicarbazepine or lacosamide or perampanel or phenobarbitone or pregabalin or retigabine or rufinamide or stiripentol or *barbit*)
#6 #4 or #5
#7 #3 and #6
(search limited to years 2005-2012)

MEDLINE and MEDLINE In-Progress (via Ovid)

1. exp Migraine Disorders/
2. (migrain* or cephalgi* or cephalalgi*).tw.
3. or/1-2
4. exp Anticonvulsants/
5. (anticonvulsant* or antiepileptic* or acetazolamide or carbamazepine or chlormethiazole or clobazam or clonazepam or clorazepate or diazepam or divalproex or ethosuximide or felbamate or fosphenytoin or gabapentin or lamotrigine or levetiracetam or lidocaine or lignocaine or lorazepam or mephobarbital or methsuximide or midazolam or nitrazepam or oxcarbazepine or paraldehyde or pentobarbital or phenobarbital or phenytoin or primidone or valproate or tiagabine or topiramate or valproic or vigabatrin or zonisamide or eslicarbazepine or lacosamide or perampanel or phenobarbitone or pregabalin or retigabine or rufinamide or stiripentol or $barbit$).tw.
6. or/4-5
7. 3 and 6
8. randomized controlled trial.pt.

9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. clinical trials as topic.sh.
13. randomly.ab.
14. trial.ti.
15. or/8-14
16. exp animals/ not humans.sh.
17. 15 not 16
18. 7 and 17

For MEDLINE: limited 18 to yr="2005 -Current"
For MEDLINE In-Process: searched current week on 15 January 2013

EMBASE (via Ovid)

1. exp Migraine/
2. (migrain* or cephalgi* or cephalalgi*).tw.
3. or/1-2
4. exp Anticonvulsants/
5. (anticonvulsant* or antiepileptic* or acetazolamide or carbamazepine or chlormethiazole or clobazam or clonazepam or clorazepate or diazepam or divalproex or ethosuximide or felbamate or fosphenytoin or gabapentin or lamotrigine or levetiracetam or lidocaine or lignocaine or lorazepam or mephobarbital or methsuximide or midazolam or nitrazepam or oxcarbazepine or paraldehyde or pentobarbital or phenobarbital or phenytoin or primidone or valproate or tiagabine or topiramate or valproic or vigabatrin or zonisamide or eslicarbazepine or lacosamide or perampanel or phenobarbitone or pregabalin or retigabine or rufinamide or stiripentol or $barbit$).tw.
6. or/4-5
7. 3 and 6
8. random$.tw.
9. factorial$.tw.
10. crossover$.tw.
11. cross over$.tw.
12. cross-over$.tw.
13. placebo$.tw.
14. (doubl$ adj blind$).tw.
15. (singl$ adj blind$).tw.
16. assign$.tw.
17. allocat$.tw.
18. volunteer$.tw.
19. Crossover Procedure/
20. double-blind procedure.tw.
21. Randomized Controlled Trial/
22. Single Blind Procedure/
23. or/8-22
24. (animal/ or nonhuman/) not human/
25. 23 not 24
26. 7 and 25
27. limit 26 to yr="2005 -Current"

WHAT'S NEW

Date	Event	Description
27 May 2016	Review declared as stable	See Published notes.

HISTORY

Review first published: Issue 6, 2013

Date	Event	Description
8 May 2014	Amended	Minor edit made to numbers reported in Results of the search.
20 June 2013	New search has been performed	Searches updated on 15 January 2013. Four new trial reports included (RR 4301-00066; RR 995-00074; RR 995-00085; Silberstein 2013), including three previously confidential research reports (RR 4301-00066; RR 995-00074; RR 995-00085). One previously included trial report now excluded (Mathew 2001, describing a post hoc subgroup analysis of RR 995-00074).
20 June 2013	New citation required and conclusions have changed	The pooled evidence derived from trials of gabapentin suggests that it is not efficacious for the prophylaxis of episodic migraine in adults. This contrasts with the findings of our previous review (Chronicle 2004; Mulleners 2008). Gabapentin enacarbil (considered for the first time in this update) is not efficacious for the prophylaxis of episodic migraine in adults.
26 August 2008	Amended	Converted to new review format.
11 May 2007	New search has been performed	May 2007 (Issue 3, 2007): • Electronic searches updated through December 2005 • Handsearches updated through April 2006 • Review revised to incorporate eight new included trials • Dr WM Mulleners took over as guarantor of the review

CONTRIBUTIONS OF AUTHORS

Prof Linde: Designing the review. Co-ordinating the review. Data collection for the review. Screening search results. Organising retrieval of papers. Screening retrieved papers against eligibility criteria. Appraising quality of papers. Extracting data from papers. Writing to authors of papers for additional information. Providing additional data about papers. Data management for the review. Entering data into RevMan. Analysis of data. Interpretation of data. Providing a clinical perspective. Writing the review.

Dr Mulleners: Conceiving the review. Designing the review. Data collection for the review. Screening search results. Organising retrieval of papers. Screening retrieved papers against eligibility criteria. Appraising quality of papers. Extracting data from papers. Interpretation of data. Providing a clinical perspective.

Prof Chronicle: Performing previous work that was the foundation of the current review.

Assoc Prof McCrory: Analysis of data. Interpretation of data. Providing a methodological perspective. Providing general advice on the review.

DECLARATIONS OF INTEREST

Prof Linde: During the process of preparing this review the author received a travel grant from Allergan in Sweden and was involved as an investigator in a clinical trial in Norway sponsored by AstraZeneca and comparing candesartan, propranolol, and placebo in the prophylaxis of migraine.

Dr Mulleners: The author was a paid consultant for the Merck Dutch Migraine Advisory Board and received a speaker's fee from Merck Sharp & Dohme Corp.

Prof Chronicle: Author deceased. During the process of preparing the original review the author was a paid consultant for Johnson & Johnson and NPS Pharmaceuticals in the USA.

Assoc Prof McCrory: During 2008, the author was a paid expert witness for the plaintiffs in a legal action against the manufacturer of Neurontin (gabapentin). In this capacity, he prepared a systematic review examining previously confidential research reports obtained from the manufacturer (through discovery), along with published trial reports of gabapentin for migraine prophylaxis, and testified at trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- International Headache Society, UK.

  Funding for administrative costs associated with editorial and peer review of the original and updated reviews
- *Lifting The Burden:* the Global Campaign against Headache, UK.

  Funding for administrative costs associated with editorial and peer review of the updated review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After reviewing the variety of methods used for calculating headache index, we decided that no systematic analysis of headache index data would be undertaken, for two principal reasons. First, rarely was sufficient information given to allow a clear understanding of how the index was calculated, and second, even when indexes were clearly described, they were not always useful — for example, because they confounded severity scores with frequency scores. Avoiding the use of headache index measures is consistent with the recommendations of the International Headache Society (Tfelt-Hansen 2012).

After publication of the protocol, we decided not to extract trial data on pain intensity, duration of attacks, or associated symptoms of migraine (nausea, vomiting, photophobia, phonophobia). The reasons were that such information was rarely given, and that the methods used were not standardised.

Our methods for assessing and dealing with heterogeneity have evolved over time in line with changing Cochrane methods. The protocol for the original review specified that we would test estimates of efficacy for homogeneity, use a fixed-effect model to combine homogenous estimates, and use a random-effects model to combine estimates when a group of studies with statistically heterogeneous results appeared to be clinically similar. In the original review itself, and in the 2007 update (Chronicle 2004; Mulleners 2008), we in fact used a random-effects model throughout for pooled analyses. In the present review, we again use a random-effects model for pooling, but we have added a possible fixed-effect sensitivity analysis in select cases; see Assessment of heterogeneity for details.

NOTES

An updated search in May 2016 only identified one relevant study (Zain 2013). However, we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Zain, S., M. Khan, et al. (2013). "Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: Randomized open label control trial." Journal of the Pakistan Medical Association 63(1): 3-7.

INDEX TERMS

Medical Subject Headings (MeSH)

Amines [*therapeutic use]; Anticonvulsants [*therapeutic use]; Carbamates [*therapeutic use]; Cyclohexanecarboxylic Acids [*therapeutic use]; Gabapentin; Migraine Disorders [*prevention & control]; Pregabalin; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [*analogs & derivatives] [therapeutic use]

MeSH check words

Adult; Humans